Long-term Anabolic-Androgenic Steroid Use, Aggression and Executive Functions

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Abstract

Anabolic-Androgenic steroids (AAS) are synthetic derivatives of testosterone. While they previously were associated mostly with use among professional athletes, the recent decades have seen a spread of AAS use to the general population. Heightened aggressiveness is one of the most commonly reported side effects of AAS use; however, the reasons behind this association have remained elusive. AAS have recently been shown to lead to neurochemical alterations in brain areas important for the regulation of aggression, as well as frontal areas important for executive functions. The aims of this study were to investigate aggression and levels of executive functioning in long-term AAS users. AAS users with long-term AAS using careers (defined here as 1 year of cumulative use or more) and non-AAS using exercisers were recruited from local gyms and via online forums. The assessment included a semi-structured interview concerning demographic data, exercise habits, self-reports of side effects and pattern of AAS use. Based on this data, estimated lifetime doses of AAS were calculated. Other aspects of pattern of AAS use were age of onset, total duration of use, concomitant drug abuse and AAS dependence. Aggression was assessed using the Buss Perry Aggression Questionnaire (BPAQ), which produces four subscales on different aspects of aggression. Executive functions were assessed using three commonly used neuropsychological tests; the Color Word Interference Test (CWIT), the Trail Making Test (TMT) and the Attentional Network Test (ANT). The results showed a significant and strong main effect of AAS use on several measures of aggression. AAS users with no history of drug abuse displayed significantly higher levels of aggression than controls. Furthermore, estimated lifetime dose, age of onset and duration of use correlated with levels of aggression. Findings on executive functions were somewhat more ambiguous. AAS users performed worse than controls on measures of executive inhibition and executive control. No differences were seen on tests of cognitive flexibility. It is concluded that AAS users display significantly higher levels of aggression compared to non-AAS using individuals, and that these levels are associated with a more severe pattern of AAS use. Furthermore, this investigation provides evidence that AAS users display lower levels of executive inhibition and control, but not flexibility. The implications of this finding for the association between AAS use and aggression are discussed, and suggestions for future research are presented.

Preface

The sample used in this investigation was drawn from the ongoing research project *Long-term androgenic anabolic steroid abuse on brain structure, cognitive functioning and emotional processing* coordinated from the Department of Physical Medicine and Rehabilitation, at the section of neuropsychology, Oslo University Hospital, Oslo, where I had my main training in the spring of 2014. I contributed to data collection by performing semi-structured interviews and neuropsychological assessments of some of the participants.

I would like to thank my supervisor, Astrid Bjørnebekk, both for introducing me to the fascinating world of anabolic-androgenic steroids research and for her indispensable guidance through the arduous, but ultimately rewarding work on this thesis. I would also like to thank Øyvind Ø. Sundseth for sharing his insights into all things neuropsychological, and for allowing me to use the office set up for me in my main training days.

Furthermore, I want to thank my family and friends, who for the last year and a half have had to suffer my continuous ramblings about every topic related to anabolic-steroids. And in the end, thanks to Kaia, who perhaps has suffered most of all…

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1 Introduction

Anabolic androgenic steroids (AAS) are synthetic derivatives of testosterone, designed to maximize the anabolic tissue building effect, compared to the androgenic effect, as well as to prolong the metabolic half-life thus increasing efficacy (Clark & Henderson, 2003). AAS has been thoroughly shown to increase tolerance for exercise (Tamaki et al., 2001) and increase lean body mass and physical strength (Hartgens & Kuipers, 2004). In addition to being used by exercisers for muscle gain, AAS are also used therapeutically in the treatment of a range of medical conditions, such as HIV, osteoporosis and hypogonadism (Quaglio et al., 2009). All AAS are thought to have some androgenic activity, and bind to the androgen receptors widely distributed throughout the brain (Clark & Henderson, 2003; Roselli, 1998; Pomerantz et al., 1985).

There are three main chemical families of AAS (Skårberg 2009; Oberlander & Henderson, 2012); C-17β-ester derivatives, usually administered orally, with a rapid effect. Examples of substances in this category are testosterone propionate, cypionate, enanthate and undecanoate. The second group, 19-nortestosterone derivatives, has a greater long-term effect and these substances are usually injected. Examples of substances in this group are nandrolone phenylpropriate, nandrolone decanoate and methenolone enanthate. Substances in the third group, 17α-alkyl derivatives, are usually taken orally.Substances in this group include stanozolol, oxymetholone, norethandrolone and danazol.

Like the AAS substances, the AAS users themselves have also been conceptualized into three different categories (Corcoran & Longo, 1992); Athletes, concerned with increasing their performance in sports; aesthetes, concerned with bettering their physical appearance; and lastly, fighting elite, use AAS to increase their fighting prowess and intimidation qualities. This last group includes career criminals, such as torpedoes, robbers and drug dealers. This categorization of course has more permeable boundaries as some users can belong to two or more of these groups. Cornford, Kean & Nash (2014), for example, interviewed AAS users with concomitant heroin use, and found that many of these individuals used AAS both as a way to fight weight-loss associated with heroin use as well as to increase their muscular strength to better function in their social context where violence and abuse is commonplace. A recent meta-analysis of the global epidemiology of AAS use found recreational sportspeople to be the group with the highest prevalence of AAS use, surpassing professional athletes, inmates/arrestees and drug users (Sagoe et al., 2014). Thus, it is evident that AAS

use is not just restricted to criminal subcultures, but may be a health concern in the general public as well.

1.1 History

Over 6000 years ago, humans discovered that castration made male animals easier to domesticate, and since then the source and effect of testosterone has been widely known (Freeman, Bloom & McGuire, 2001). The first scientist who tried to exploit the masculinizing effect of testosterone was the psychologist and neurologist Charles-Édouard Brown-Séquard, who injected himself with a fluid prepared from extracts from the testicles of guinea pigs and dogs. Consequently he reported rejuvenation, increased sexual prowess, increased mental capacities and appetite, although questions have been raised concerning the biological basis for these claims (Dotson & Brown, 2007).

Testosterone was first isolated and characterized in Germany in the 1930s, and soon several derivatives and similar compounds were synthesized to what is now known as anabolic androgenic steroids (Kanayama, Hudson & Pope, 2009a). There exists anecdotal evidence that German soldiers during world war II were given AAS to increase their aggressiveness in combat, and that concentration camp survivors were given AAS to rebuild muscle mass (Wade, 1972). AAS use quickly spread to professional athletes, and in 1954 AAS were used by the Russian team in the weightlifting championship in Vienna (Wade, 1972). In the 1980s AAS use began to spread outside the confines of professional sports, and the general public saw the release of handbooks on AAS use, such as Daniel Duchaine's *Original Underground Steroid Handbook*, and Nathan Philips' *Anabolic Reference Guide* (Kanayama, Hudson & Pope, 2008). Today, there is evidence to support the effects AAS have on increasing lean body mass, muscle size and strength (Evans, 2004). On the other hand, AAS is well known to produce adverse psychiatric and social effects (Oberlander & Henderson, 2012). A diverse range of medical side effects has also been associated with AAS use, such as hepatic problems, impotency, gynecomastia and cardiovascular disorders (Hartgens & Kuipers, 2004; Golestani et al., 2011). AAS use evidently is a double-edged sword.

The association between AAS and acts of violent aggression first caught the public's eye in the United States in the late 1980s, with the advent of case-reports involving grisly acts of violence committed by young AAS-using men with no prior history of violence (Thiblin, Nyberg & Moberg, 2013).

1.2 Epidemiology/prevalence:

A recent report about AAS use in Norway (Sandøy, 2013) concluded that lifetime prevalence in studies of AAS use in Norway tend to hover around 2 %. In the material for SIRUS' report, 0.6 % of adolescents and 1.6 % of young adults reported having used AAS, and men report significantly higher prevalence than women. The nature of their use was assessed with questions regarding frequency of use and use within the last six months. Among adolescents 37 % of those who reported AAS use had done so 1-4 times, while 35 % had used AAS more than 25 times. Half of them had not used AAS within the last six months. Similar rates were obtained for young adults. The willingness to use AAS to get a muscular body was also assessed; 7.0 % of the men and 2.2 % of the women reported that they would to some extent be willing to use AAS, even considering the potential health risks. Pallesen and colleagues (2006) found prevalence rates of 3.6% for boys and 0.6% for girls among 1351 high school students in Hordaland, Norway. In addition to this, they found that 27.9% reported having at least one acquaintance that used or had used AAS. It should be noted that these studies may underestimate the prevalence of AAS as the samples are young quite young. One study of 1,955 AAS users showed that the majority initiated AAS use after adolescent, with a mean age of onset of 25.81 (SD=8.26) years (Cohen et al., 2007), indicating that studies of adolescents and young adults may not be the most appropriate source of information about the prevalence of AAS use in the general population.

Concerning the global epidemiology of AAS use, Sagoe and colleagues (2014) in a meta-analysis found overall life time-prevalence to be 3.3%. Prevalence for men was significantly higher than for women (6.4% vs. 1.3%). They also found a higher prevalence among younger (<=19 years old, p%=2.5) than older participants (>19 years old, p%= 1.9). These authors also found prevalence rates to vary between regions, with Asia being the region with the lowest prevalence rates (0.2%). The large majority of AAS users are men that are recreational sportspeople (Sagoe et al., 2014; Ip et al., 2011).

Some evidence seems to indicate that AAS use has been on the rise for the last 10-15 years. Lood and colleagues (2012) found that the number of inmates who was detected using AAS increased dramatically from 1999 to 2009. Sagoe and colleagues (2014) also reported a steady increase in the global prevalence of AAS use from the 1990s to the 2000s.

Taken together, prevalence rates of AAS use vary by region and study (Sagoe et al., 2015), and it has been on the rise for the last 10-15 years. This steady increasing prevalence rate is a cause for concern considering the wide range of health issues associated with AAS

use (Golestani et al., 2011; Oberlander & Henderson, 2012). The relatively high prevalence of AAS use among adolescents (Harmer, 2010) is especially troubling in light of evidence about the impact of adolescent AAS initiation on brain development and social behaviors later in life (Schulz et al., 2004; Salas-Ramirez, Montalto & Sisk, 2010, Cunningham, Lumia & McGinnis, 2013), although some evidence indicate that most AAS users initiate use after adolescence (Cohen et al., 2007). The variation in prevalence rates as well as the inherent biases concerning self reports of performance enhancing substances (Kanayama, Pope & Hudson, 2001) make it difficult to draw strong conclusions regarding the prevalence of AAS use in the general population.

1.3 Pattern of use

Unlike use of many other illicit drugs, the use of AAS is often elaborately planned in advance. A typical pattern of use includes periods of about 6-12 weeks on AAS, called "cycles", followed by a period without use in order to minimize adverse side effects (Brower, 2002). Within these "cycles", AAS users employ techniques called "plateauing" and "pyramiding". Plateauing involves using a substance for some time, and then replacing it with another in order to reduce tolerance to a particular substance. Pyramiding involves beginning cycles with relatively small weekly doses, and then continually escalating the number and quantity of AAS substances until a maximum dose is reached either at the middle or toward the end of the cycle (Trenton & Currier, 2005). It is not surprising then, that the majority of AAS users report consumption of a wide variety of different AAS substances, and rarely sticks to one or two. In order to escape periods of hypogonadism associated with withdrawal symptoms such as decreased or absent libido, erectile dysfunction and symptoms of depression (Kanayama et al., 2015), many AAS users employ the practice of "cruising". This involves continually using low doses of AAS between cycles

Another common feature of AAS use is polypharmacy; combining AAS use with other substances, either to increase the effects of AAS or combat the negative side effects of AAS (Sagoe et al., 2015). Substances commonly used in combination with AAS include other performance enhancing drugs (Kanayam & Pope, 2012), but AAS use is also highly associated with use of recreational drugs of abuse (Buckman, Farris & Yusko, 2013). Opioid use is especially prevalent among AAS using individuals (Kanayama, Hudson & Pope, 2009a; Nyberg & Hallberg, 2012). Alcohol consumption is also highly prevalent in AAS users

(Dodge & Hoagland, 2011; Pallesen et al., 2006). AAS use, then, is apparently not associated with a healthy athletic lifestyle.

1.4 AAS dependence

In recent years, it has been increasingly recognized that AAS users may develop a dependency toward AAS (Kanayama et al., 2009a). As no instances of AAS dependence have been identified in persons treated with therapeutic doses (Brower, 2002) the risk for developing a dependency seems to be constricted to users of supraphysiologic doses. Many who have used AAS in the course of their life only go through a couple of cycles, amassing to less than 12 months of cumulative use, while others develop a pattern in which they continue using without off-periods between cycles, or "off" periods with relatively smaller doses of AAS (i.e. cruising; Kanayama et al., 2009a). Contrary to many other illicit drugs, AAS does not lead to rapid increases in dopamine levels, causing a euphoric feeling (van Amsterdam, Opperhuizen & Hartgens, 2011). The rewards of AAS use come in a more delayed fashion, as larger muscles (Kanayama et al., 2009b). Negative reinforcers of AAS have also been identified, experienced during withdrawal. These include steroid craving, fatigue, depressed mood, restlessness, loss of appetite, insomnia, reduced sex drive, headache and muscle and joint pain (Brower, 2002; van Amsterdam, Opperhuizen & Hartgens, 2011; Quaglio et al., 2009). Many users also report fear of losing muscle mass, physical strength and physical attractiveness to be concerns over cessation of AAS (Cohen et al., 2007). Thus, both negative and positive reinforcers can work in tandem to create a dependence-syndrome in some AAS users. The prevalence of dependence among AAS users has been estimated to be as high as 30 % (Kanayam et al., 2009a).

1.5 AAS as a general health problem

Sandøy (2013) concludes that prevalence rates for Norway tend to hover around 2 %, and reports that about a third of self-reported AAS users had used AAS more than 25 times. Long-term AAS use, then, is apparently not highly prevalent in Norway, although one has to consider the possibilities of underreporting (Kanayama, Pope & Hudson, 2001). The estimated extent of a public health problem should not solely be based on its prevalence though. It should also take into consideration the severity of the problem for those it may concern as well as a closer evaluation of *who* it really does concern. The by now widely

accepted association between AAS and aggression (Trenton & Currier, 2005) indicates that, while AAS use may be detrimental for the user itself, individuals in close proximity may also be at risk for side effects of AAS use (e.g. significant others; Choi & Pope, 1994). These individuals are not covered in prevalence studies. Taken together, the extent of AAS use as a public health problem may be larger than low prevalence rates might imply.

1.6 Aggression

The concept of aggression is multifaceted and wide. As it is a central theme in this investigation, it is worth closer scrutiny. A wide variety of different definitions of aggression have been proposed, but generally it has been classified into two distinct subtypes (Ramirez & Andreu, 2006); hostile aggression, in which the intent of the aggressive behavior is harm or distress toward the target of the aggressive behavior, and instrumental aggression, in which aggression is used more indirectly as a tool to achieve some reward or profit. The former is seen as more impulsive, affective and thoughtless, while the latter is considered more though out and cold blooded. A tripartite division of aggression into behavior (physical and verbal aggression), emotion (feelings of anger) and cognition (hostility, ill will) has been suggested as an expansion of aggression beyond behaviors (Buss & Perry, 1992).

A framework called the I^3-theory (pronounced I-cubed) has been proposed to help researchers understand how a wide range of risk factors act and interact in social interactions that may or may not lead to aggressive outcomes (Slotter & Finkel, 2011). This theory describes how three classes of factors influence the processes that may lead to aggressive behaviors. These factors are: Instigating factors (e.g. insults, goal obstruction, social rejection) that may trigger a hostile situation. Impelling factors (e.g. personality characteristics, attitudes, beliefs) that determine the strength of the aggressive impulse experienced by the individual. Finally, inhibiting forces (e.g. dispositional self-control, negative beliefs about aggression) are factors that determine whether the individual will override the aggressive impulse and reconsider the use of aggression. I^3-theory also states that these factors interact with one another, across classes. This view was supported by a series of studies that tested hypotheses derived from the I^3-theory, concerning how these classes of factors interact to produce intimate partner violence (Finkel et al., 2012). In one of these studies, 50 couples were measured on trait aggressiveness (Impelling factor), inhibition (a computerized Stroop task; Inhibitiong factor) and completed a questionnaire diary at home about how much their partner had provoked them that day (Instigating factor). Intimate partner violence was

assessed once a day, by presenting each participant with a computerized voodoo doll representing their partner and counting the number of pins they chose to insert into the doll. Results indicated that all three factors interacted to promote partner violence; more provocative behavior than usual, high trait aggressiveness and low executive inhibition interacted to increase the number of pins inserted into the virtual voodoo doll.

1.7 AAS and aggression

1.7.1 Results from animal studies

The major methodological advantage of using animal models when investigating the association between AAS and aggression is that researchers can control for pattern of use in the subjects. At the same time, this is a weakness, in that it does not accurately reflect human AAS use patterns (McGinnis, 2004). Thus, many animal studies use a "cocktail" of different AAS in order to more accurately mirror human use, but then again, this hinders the task of determining individual AAS effects of different substances (Lumia & McGinnis, 2010). Another major methodological advantage is the ability to randomly assign subjects to AAS use conditions.

Long-term AAS use initiated during adolescence has been shown to increase aggressive responding in rats (Olivares et al., 2013, Long et al., 1996; Farrell & McGinnis, 2004; Salas-Ramirez, Montalto & Sisk, 2010; Salas-Ramirez, Montalto & Sisk, 2008; Wood et al., 2013). A study that directly compared long-term AAS use and aggressive responding in rats treated during adolescence and adulthood, found equally high levels of agonistic aggressive responses in both groups compared to controls. However, they observed significantly less submissive responses (such as escape-dashes) in rats treated during adolescence (Salas-Ramirez, Montalto & Sisk, 2010). Salas-Ramirez, Montalto & Sisk (2008) also compared the acute effect of AAS on aggression in adults versus adolescents, and found significantly higher levels of aggressive responding in adolescents compared with adults. In this study, the difference in aggression between adults treated with AAS compared to controls, only tended toward significance. They concluded that the adolescent brain might be more vulnerable to the effects of AAS on the central nervous system than the adult brain.

Several studies have investigated neurochemical alterations following AAS use. AAS binds to the androgen receptors, found in the amygdala, hypothalamus, the stria terminalis, hippocampus, cingulated cortex, parietal cortex and cerebellum of rhesus monkeys

(Abdelgadir et al., 1999). Some AAS can also be aromatized into estrogens with agonistic activity at the estrogen receptors, found throughout the brain (Henderson et al., 2006; Panetti, Porter & Henderson, 2009; McEwen, 2001). Both androgens and estrogens have been shown to play important roles in aggression in mice (Sato et al., 2004; Scordalakes & Rissman, 2003). Chronic exposure of AAS in rats has been shown to lead to both acute and chronic alterations in GABAergic responding in the forebrain of mice (Henderson et al., 2006). Furthermore, this effect was dependent on the dose of AAS administered. This alteration has been shown to be modulated by both androgen and estrogen receptors (Penatti, Porter & Henderson, 2009). Hamsters exposed to AAS during adolescence have been found to display increased activity of vasopressin in the ventrolateral hypothalamus, the stria terminalis and lateral septum, brain areas associated with modulation of aggression (DeLeon, Grimes & Melloni, 2002). Thus, it is evident that AAS may act upon a wide variety of neurochemical systems in brain areas associated with modulation of emotional behavior and aggression, and that there is a complex relationship between the chemical structure of the AAS, exposure dose and age of the subject.

The effects of AAS in combination with recreational drugs of abuse have also been investigated in animals. Long & colleagues (1996) treated rats with either an AAS (nandrolone), cocaine or a combination of these substances over a four week period. They found that rats receiving a combination of AAS and cocaine displayed increases in aggressive responding compared to rats treated with either substance alone. A comparable investigation has been done with nandrolone and amphetamine use (Steensland et al., 2005). These authors found that rats first treated with nandrolone, showed increased aggressive responding when treated with amphetamine three weeks after cessation of AAS injection, compared to rats only treated with amphetamine.

Aggressive responding induced by AAS has also been shown to be dependent on the chemical structure of the AAS substance (McGinnis et al., 2002; Breuer et al., 2001). McGinnis and colleagues (2002) found that Testosterone Propionate (TP) increased aggression in adult male rats, while Nandrolone-treated (ND) rats did not differ from controls, and rats treated with Stanozolol (ST) actually decreased aggressive responding. ND was found to increase aggressive responding in male rats in an earlier study (Long et al., 1996), however, the authors of this study also noted that the effect of this particular AAS substance on aggression was smaller in magnitude than that observed with other AAS substances in earlier studies (Long et al., 1996, p. 850). A more recent investigation has also failed to show

an increase in aggression following ND-treatment (Wesson & McGinnis, 2006). Concerning the surprising finding that ST decreased aggressive responding, this has been corroborated in other studies (McGinnis et al., 2002; Breuer et al., 2001; Farrell & McGinnis, 2004; Martinez-Sanchis et al., 1996; Wesson & McGinnis, 2006).

A recent investigation sought to illuminate some of the causal pathways between AAS use and aggression. Wood and colleagues (2013) investigated the effect of AAS on aggressive motivation and impulsivity. They found no increase in aggression motivation in AAS treated rats, as seen by their unchanged willingness to allow an intruder rat into their cage compared to vehicle treated rats. Impulsivity was lowered in rats treated with AAS, measured by an increased preference of a larger, delayed reward. These findings indicate that AAS induced aggression is not a result of an increased desire to fight or loss of impulse control.

There seems to be evidence in favor of the proposition that AAS may alter social cognitive processing in rats. McGinnis and colleagues (2002) in the study mentioned above found that AAS (TP) treated rats reacted significantly more aggressively than vehicle treated rats in response to physical provocation directed at the intruder rat. AAS treated rats have also been shown to react more defensively in response to relatively harmless stimuli (the experimenter's hand) and show more fear reactions to other harmless stimuli (e. g. slight air puff in the back; Johansson et al., 2000).

Taken together, evidence for the effect of AAS on increased aggression has been thoroughly substantiated in animal research. Adolescent AAS exposure has been shown to produce a heightened level of aggression both acutely (Salas-Ramirez, Montalto & Sisk, 2008) and in adulthood (Olivares et al., 2013, Farrell & McGinnis, 2004) as well as qualitatively different aggressive behavior, with fewer submissive responses compared to adult exposure (Salas-Ramirez, Montalto & Sisk, 2010). Evidence concerning the acute effects of AAS on aggression in adult exposure is more ambiguous than evidence on adolescents (Sala-Ramirez, Montalto & Sisk, 2008). There is also some evidence for an interaction between AAS use and use of other illicit substances (Long et al., 1996; Steensland et al., 2005), and that AAS induced aggression is not caused by an increased motivation to fight or lowered impulsivity (Wood et al., 2013). A kaleidoscopic picture emerges, with complex relationship between the chemical structure of the AAS substance, age of AAS exposure, sex of the AAS user and possible alterations in social cognitive processing.

1.7.2 Experimental studies in humans

Experimental studies of AAS use in humans are restricted by ethical considerations that limit the conclusions that can be drawn from them. Firstly, one cannot ethically conduct an experiment where the doses administered are as large as those that have been observed in real-life AAS users. Secondly, the length of use duration utilized in experimental studies cannot possibly approximate real situations where AAS users have been known to use for decades. On the other hand, experimental studies are unmatched in their ability to inform us about the causal links between acute and short term AAS use and aggression. This is a powerful advantage that makes the few studies of this kind invaluable sources of knowledge concerning the relationship between AAS use and aggression.

The first prospective, double-blind, placebo-controlled study to investigate the effects of AAS on mood was performed in the early 1990s (Su et al., 1993). In this investigation, 20 healthy volunteers were given, in bulks of three days per condition, first a placebo-baseline, then low AAS dose (40 mg methyltestosterone/day), high (240 mg methyltestosterone/day) followed by a placebo-withdrawal phase. These authors thus measured the acute effects of AAS use. When in the high-dose condition, participants reported significantly increased levels of self-reported irritability and distractibility, while violent feelings and anger showed a trend toward significance. Pope, Kouri and Hudson (2000) used a randomized, double blind experimental design to investigate the effects of AAS use, mania and aggression. They injected study participants with either testosterone or a placebo control with increasingly higher doses, ranging from 150 mg/week to 600 mg/week, over six weeks and measured aggression using the Buss Perry Aggression Questionnaire (Buss & Perry, 1992) and the Point Subtraction Aggression Paradigm (PSAP, Cherek et al., 1996). Manic symptoms were measured using the Young Mania Rating Scale (YMRS, Young et al., 1978) as well as daily diaries at home, to be filled out by both participants and significant others. The results from this investigation showed that participants showed significantly increased measures of manic symptoms as well as aggression, as measured by the PSAP. However these findings were not uniform as most participants showed no significant change while a few showed marked changes. The participants showed no significant changes in aggression measured by the Buss Perry Aggression Questionnaire except the Verbal Hostility subscale. The results were unrelated to the participants' previous exposure to AAS or regular weight lifting, but participants displayed elevated symptoms with higher dosages. Another study (Tricker, Casaburi et al., 1996) found no relationship between AAS exposure and aggression or

changes in mood, however this investigation also used relatively small doses (600mg testosterone enanthate/week), as well as only one AAS substance, compared to the wide variety of combinations often reported by real life AAS users. These authors conclude that the findings could also be a result of their strict screening procedure, excluding people with sings of previous psychiatric or drug problems.

Taken together, these studies are informative concerning the acute effects of moderate (Pope, Kouri & Hudson, 2000) to high (Su et al., 1993) doses of AAS. However, as seen in these studies the use of lower doses seems to produce less severe symptoms, which might indicate that the results tend to underestimate the effects of real-life AAS use. The main point is that short-term AAS use seems to increase levels of aggression in a dose-dependent manner.

1.7.3 Naturalistic studies

Unlike experimental studies, naturalistic studies can investigate the effects of long-term AAS use. Like experimental studies, however, naturalistic studies also have some inherent methodological concerns, some of which might be considered more troublesome when investigating the association between AAS and aggression. One can hypothesize that social desirability bias may be especially common in these studies (Saunders, 1991). Although naturalistic studies necessarily are only correlational, impeding the causal conclusions regarding the relationship between AAS use and aggression that can be drawn from them, they nonetheless serve to illustrate the need to further elucidate the nature of this relationship.

Case studies were the earliest source of insight on the apparent relationship between AAS use and aggression and violent acts (Thiblin, Nyberg & Moberg, 2013). Pope and Katz (1990) interviewed three AAS users who attributed their violent behaviors, including murder, to their use of AAS. Another early case report (Dalby, 1992) describes a young man, who following a five week period of increasing doses of the AAS Equipoise, experienced a significant change in personality that persisted long after cessation of AAS use, and that culminated in armed robbery. Pope and colleagues (1996) reported a case in which a 16-year-old boy was convicted of killing his 14-year-old girlfriend following AAS use. This boy had no record of antisocial behavior prior to AAS use, but when he used steroids he showed a striking change of character and started to get in trouble with the police. These authors also described how a 27-year-old man intently used AAS to increase his confidence and feeling of invincibility needed to deal heroin, and that he would not be able to do this without AAS. An

investigation of two pairs of monozygotic twins, where one twin used AAS and the other did not, showed increased levels of hostility, aggressiveness and paranoid ideation in the AAS using twins (Pagonis et al., 2006b). Cooper and Noakes (1994, cited in Trenton & Currier, 2005) longitudinally observed 12 bodybuilders using AAS, who displayed increases in antisocial behavior including violence and a tendency towards illegal and dangerous activities.

Based on anecdotal evidence that partners of AAS users are at risk of becoming victims of AAS induced aggression, one study found that AAS users reported significantly more fights, verbal aggression and violence toward their wives and girlfriends when on AAS compared when off AAS a and compared to non-AAS using controls (Choi & Pope, 1994). Thiblin and Pärlklo (2002) performed a prospective longitudinal follow-up of police records of five known users of AAS, for which AAS use was the first illegal activity reported to the police. All of these participants were later convicted for more serious crimes, such as assault and drug dealing. This study is interesting in that the authors found that AAS use not only caused violent outbursts of impulsive aggression, but also marked an entry into criminal careers possibly catalyzed by AAS use.

A recent study from Norway (Jenssen & Johannessen, 2014) investigated whether contemplation of AAS use in itself was a risk factor for aggression. Four hundred students in Norwegian high schools (mean age; 16,8 years) completed questionnaires concerning AAS use and aggression (Aggression Questionnaire, Buss & Perry, 1992). Of these, 16 (4.0%) reported prior AAS use and 20 (5.1%) reported contemplating AAS use. These groups were compared to each other and the remaining students. Students who had previously used AAS, and contemplators reported significantly elevated levels of aggression compared to non-users, but the results failed to show a significant difference between users and contemplators. Thus, merely contemplating AAS use was a strong predictor for increased aggression as AAS use in itself.

1.7.4 AAS and criminal offending

A higher level of aggression in AAS users may ultimately manifest itself as various types of criminal offending, associated with personal suffering as well as great costs to society. The assessment of the relationship between AAS use and criminal offending is therefore an important area of research.

Beaver, Vaughn and Wright (2008) found a significant relationship between lifetime AAS use and involvement in acts of serious violent behavior (e.g. physical fights, stabbings) in young men, when controlling for age, previous antisocial behavior and concomitant drug use. Another investigation found an increase in criminal activity among users of AAS, with a concurrent misuse of other illegal drugs following onset of AAS use (Skårberg, Nyberg & Engström, 2010). In this study, onset of any type of drug increased the level of criminal offending, but onset of AAS use led to a sharper increase in criminal behavior. AAS has been shown to have an increased prevalence among substance users convicted of violent crimes compared to substance users committed of non-violent crimes (Lundholm et al., 2010). Lood and colleagues (2012) performed AAS screening on a total of 12 141 urine samples from suspects in police cases (6362 samples) and inmates in prison (5779 samples) over a period of ten years. AAS were detected in 33.5% of persons involved in petty drug offences, 38.8% in cases of driving under the influence of drugs and in 19.4% of cases involving violent crimes. On the other hand, a recent investigation cast doubt on the relationship between AAS and criminality (Lundholm et al., 2015). This investigation found that the strong association between AAS use and violent offending was reduced to non-significance when controlling for use of other substances. Controlling for IQ, psychological functioning (stress coping), ADHD, personality disorders and childhood socioeconomic status did not diminish the association further. Taken together, there are now several studies that show AAS use is prevalent in individuals convicted for various crimes, especially crimes involving drugs and violent offending. There is also evidence that indicates that AAS use in addition to use of other illicit drugs of abuse is a risk factor for increased rates of violent offending.

There is an apparent discrepancy between qualitative studies where AAS tend to be highly associated with acts of violence, and quantitative studies which tend to be less conclusive concerning the strength and exclusivity of this association. This has been attributed to either to a low frequency of acts of violence in AAS users, or a link between AAS and violence which in some way masks this association in quantitative studies (Thiblin, Nyberg & Moberg, 2013). These authors suggest that AAS in and of itself might not be a powerful risk factor for acts of violence, but that a chronic AAS abuse might lower the threshold for committing these acts under the influence of other substances, such as alcohol and other drugs of abuse.

1.8 Executive functions and aggression

Executive functions are top-down mental processes that among other things are important for impulse control, mental flexibility and selectively paying attention. Humans rely heavily on executive functions to successfully navigate the extreme complexity of human society. Three core executive functions have been identified (Diamond, 2013): Inhibition, working memory and cognitive flexibility. Briefly; inhibition pertains to the ability to control attention, behavior, thoughts and emotions, and instead use top-down processing to choose how to react to stimuli. Without inhibitory control, we would be unable to resist impulses and automatic responses. An aspect of inhibition that is of interest in the present discussion is self-control; being able to control one's behavior. Working memory pertains to ability to hold and manipulate information in the mind (Baddeley & Hitch, 1994). Lastly, cognitive flexibility is the ability to mentally change perspectives, both spatially and interpersonally, as well as adjusting behavior in response to changing circumstances. While executive functions have been divided into these three domains, there is a heavy interdependency between them. Few, if any, cognitive tasks rely only on one kind of executive function (Diamond, 2013). For example, when cognitively shifting between two rule sets, you have to keep both sets in working memory, and use inhibition to inhibit the rule not currently in use.

There is now a large research literature that demonstrates the importance of executive dysfunction in criminal offending. Although this field is trouble ridden with varying definitions and measurements of both executive functions and aggression, the common theme is that executive dysfunction, however defined, is related to criminality (Hancock, Tapscott & Hoaken, 2010). Domestic violence has been related to poorer performance on Trail Making Test B, compared to controls (Becerra-Garcia, 2015), and impaired executive functions in patients following Traumatic Brain Injury (Marsh & Martinovich, 2006). One study of criminal offenders found that performance on the inhibition condition of the Stroop task was significantly related to frequency and severity of violent offending, but not related to nonviolent offending (Hancock, Tapscott & Hoaken, 2010). Broomhall (2005) found impairments in inhibition and flexibility, as measured by respectively the Stroop 3 and 4, in offenders of reactive (impulsive, unplanned) and not instrumental (goal-directed, planned) aggression. One area of some dispute is whether executive dysfunction is more characteristic of violent offenders or of all individuals who engage in some form of criminal behavior (Hancock, Tapscott & Hoaken, 2010).

Impairments in executive functions have also been linked to aggression in the general population. Poorer inhibition has been found in persons with high trait aggression compared to persons with low trait aggression in a stop signal task with emotional stimuli (angry faces; Pawliczek et al., 2013). Set-shifting impairments have been associated with anger rumination and revenge planning (Gul & Ahmad, 2014). In the perspective of the I^3-theory, executive inhibition has been labeled an inhibiting factor; high levels of executive inhibition can work to inhibit further escalation in an aggression filled situation by recruiting down-stream processing to override aggressive impulses (Slotter & Finkel, 2011). In support of this view is Finkel and colleagues (2012) in the study mentioned above, where a higher level of inhibition (better performance on a computerized version of the Stroop test) repressed the level of violence toward a virtual voodoo doll representing the person's intimate partner.

1.9 AAS and executive functions

1.9.1 Evidence from human studies

Only two studies have to date investigated the effects of long-term AAS use on cognition in humans. Kanayama et al. (2013) conducted a study where they performed neuropsychological assessment of long-term AAS users using the CANTAB-battery (Cambridge Cognition). They found no significant differences on the modules Choice Reaction Time, Rapid Visual Information Processing or Verbal Recognition Memory, which implies that psychomotoric speed, vigilance, sustained attention and verbal memory was not related to AAS use. On the test Pattern Recognition Memory AAS users made significantly more errors on immediate recognition compared to nonusers. This study provided the first evidence that long-term AAS use is associated with lower levels of cognitive functioning in some cognitive domains. Especially interesting was the finding that long-term AAS users displayed lower functioning on tests tapping working memory, an aspect of executive functioning, and the finding that the scores on these tests were negatively correlated with lifetime AAS dose.

Hildebrandt and colleagues (2014) compared on-cycle vs. off-cycle AAS users on measures of inhibitory control using an affective go/no-go task, and found on-cycle users to make more errors but respond faster than off-cycle users in response to emotional stimuli. This somewhat unexpected result was explained by a generally higher brain arousal, associated with heightened emotional reactivity, locomotion and alertness. They also found some differences on a computerized set-shifting task, indicating that on-cycle AAS users may

be poorer at planning and set-shifting. Findings from this study were interesting, however the samples used were very small (N=5 to 6), and must thus be considered preliminary.

1.9.2 Evidence from animal studies

While the literature on AAS and executive functions is sparse in animal models, it is somewhat less incomprehensive than the literature on humans. AAS has been shown to be associated with alterations in dopamine function in the prefrontal cortical-striatal circuitry (Wood et al., 2013). This alteration has also been noted in a study on the effect of AAS on dopamine response to cocaine (Kurling-Kailanto, Kankaanpää & Seppälä, 2010). The prefrontal cortical-striatal circuitry is important for executive functions, such as behavioral flexibility (Wallin & Wood, 2015) and risk-reward decision making (Simon et al., 2011). Alterations in this circuit may have implications for other tasks performed by the prefrontal cortices (Wallin & Wood, 2015). AAS use has also been shown to lead to alterations in brain nerve growth factor and GABAergic transmission in the forebrain of rats (Pieretti et al., 2012; Henderson et al., 2006). Wallin and Wood (2015) tested the assumption that AAS use may lead to a decrease in behavioral flexibility. These authors used a set-shifting and reversal learning paradigm on adolescent male rats. The results from this investigation showed that rats treated with AAS required significantly more trials to reach the criterion on several set-shift tasks, and thus were impaired on behavioral flexibility compared to controls.

A few studies have investigated the general effect of AAS on brain and cognition. As noted, the main point of action for AAS in the central nervous system are the androgen receptors and to a lesser extent the estrogen receptors (Clark & Henderson, 2003). These receptors are found in many areas of the brain important for memory and learning, including the prefrontal cortex (Janowsky, 2006). Brännvall et al. (2005) found that nandrolone inhibited the proliferation of neural stem cells and neurogenesis in the dentate gyrus in adult rats. These authors conclude that nandrolone may have long-term consequences on cell recruitment in the brain. Specifically inhibiting neurogenesis in the dentate gyrus of adult rats has been associated with impaired spatial and recognition memory (Jessberger et al., 2009), providing a possible mechanism for the impairments seen in these capacities in rats treated with AAS compared to vehicle. Living in an enriched environment and exercise has been shown to increase neurogenesis in dentate gyrus in rodents (Kempermann, Kuhn & Gage, 1997; Brown et al. 2003; Bjørnebekk, Mathé & Brené, 2005) and improve spatial memory in

adult rats (Nilsson et al., 1999). A recent animal study has shown that this positive effect of exercise might be ameliorated by the use of AAS (Novaes Gomes et al., 2014).

Taken together, the few studies that have investigated the association between AAS use and executive functions have shown AAS to lead to neurochemical alterations in brain regions important for executive functions (Pieretti et al., 2012; Kurling-Kailanto, Kankaanpää & Seppälä, 2010). Preliminary evidence has indicated that acute AAS-intoxication may be associated with poorer planning and set-shifting, and an increased emotional reactivity in humans (Hildebrandt et al., 2014), and a decrease in behavioral flexibility in rats (Wallin & Wood, 2015).

2 Aims and hypotheses

AAS use is widely used among the general population (Sagoe et al., 2014) and increased aggression is a commonly reported side effect of AAS use in both humans (e. g. Pope, Kouri & Hudson, 2000; Thiblin, Nyberg & Moberg, 2013) and animals (e. g. Olivares et al., 2013, Long et al., 1996), although the causes for this association remains largely elusive (Wood et al., 2013). Some evidence also indicate that AAS may have negative effects on brain maturation (Cunningham, Lumia & McGinnis, 2013), executive functions (Wallin & Wood, 2015; Kanayama et al., 2013) and brain areas important for executive functions (Pieretti et al., 2012; Kurling-Kailanto, Kankaanpää & Seppälä, 2010). The aims of this investigation are to elucidate the effects AAS pattern of use on aggression and executive functions. The hypotheses for this study are as follows: 1. Long-term AAS use is associated with increased levels of aggression. 2. Long-term AAS use is associated with lower levels of executive functions. 3. Aggression in AAS users is related to pattern of AAS use. 4. Lower levels of executive functions are related to pattern of use.

3 Methods

3.1 Study participants

The sample was drawn from the ongoing research project *Long-term androgenic anabolic steroid abuse on brain structure, cognitive functioning and emotional processing* coordinated from the Department of Physical Medicine and Rehabilitation, at the section of neuropsychology, Oslo University Hospital, Oslo. The participants in the study are male weightlifters belonging to one of the following groups: Men reporting at least one year of cumulative AAS use and men who have never tried AAS.

Participants were recruited through posts on Internet forums concerning bodybuilding, strongman, fitness and weightlifting, and forums (open and closed) that directly target steroid users. Recruitment also occurred through advertising on a Facebook project page. Posters and flyers were distributed on selected gyms, and participants in the study were given flyers and encouraged to spread the word about the study to potential candidates. In order to catch the attention of the right people we chose the following headline on the recruitment material and advertisements: "Ever bench-pressed 120kg?". In the recruitment information the study aim was explicitly stated. For the AAS group we sought both current and previous users having used AAS over time, and at least exceeding one year of cumulative use. For the control group we sought men who spend much time on strength training (weight lifting) with no experience with AAS or equivalent doping substances. The participants were compensated for their participation with 1000NOK (~125 USD).

In total 159 men participated in the study divided into 87 current or past AAS users, and 69 non-using controls consisting of men who either were using considerable amount of time on weightlifting and/or who classified themselves as highly experienced power lifters competing at a national level. Two users did not entirely fulfill our inclusion criterion, in that they only had close to one year of cumulative AAS use, and one control had very little experience with strength exercise. They were nonetheless included in this investigation, as these criteria were as strict as they were because of the MR-data not included in the present paper. A total of 6 controls and 14 users failed to deliver their BPAQ questionnaires. The final sample in the analyses of differences in aggression was thus 63 controls and 73 AAS users. Data on the Trail Making Test and Color Word Interference Test were missing for two AAS

users, analyses on executive functions, then, will include 69 controls and 85 AAS users. The ANT was completed by 66 controls and 83 users.

3.2 Assessment procedure

The study evaluation included questionnaires the participant had filled out beforehand, which were delivered at the start of the evaluation to the investigator. Then followed an interview about exercise habits, medical and psychiatric disease history, use of medications (specifying psychotropic drugs), drug and alcohol use and other potential risk factors regarding cognition, such as head trauma or encephalitides. Participants belonging to the user group were interviewed about the nature of their AAS use. The cognitive evaluation followed after the interview. Lastly, the participants were given the MCMI-III (Millon, 1994) to be filled out at home and returned via mail. The entire assessment lasted for about three hours, with some 30 minutes more for AAS users due to the interview regarding their AAS use and the SCID module on AAS-dependence.

3.3 Interview assessment

The interview evaluation consisted of a semi-structured interview concerning the participants' exercise habits, i.e. number of weightlifting vs. endurance training sessions per week, their personal records in bench press, deadlift and squat, and any achievements in sports they have participated in. They were asked about any previous head trauma or substance abuse that might influence cognition. Participants in the user group were also asked about the nature of their AAS use, such as age of onset, number of lifetime cycles, number of years of AAS use and an estimation of average weekly AAS dose within cycles. They were also asked whether they had ceased using AAS, and if not, where in the cycle they were presently (at the time the assessment took place). Any medical, emotional or cognitive side effects they had experienced were also recorded. Then a module from SCID II (First et al., 1997), assessing AAS dependence (Pope, Kean et al., 2010) was administered. This module has shown promising psychometric properties in the preliminary study by Pope, Kean and colleagues (2010).

3.4 Estimated lifetime dosage

Estimated lifetime doses of AAS in milligrams were calculated using the obtained information about AAS pattern of use (e.g. cycle duration, number of cycles, years of use, any cessation of use, estimated weekly dosage etc.). For most participants this was easily calculated as their AAS use was carefully planned for and implemented according to the plan. Some users, however had not equally good overview or were just not very systematic about their usage habits. They could have used large quantities over a long period of time, but the pattern of use was more guided by spontaneity or what preparations they had access to at the moment, rather than by a usage plan. Some reported they had use for so long that they had lost track of their history of use. For these participants it was harder to calculate a thought lifetime dose (and accordingly for a few this value is missing (n=4)). However for most we have made an attempt based on the available information. It is thus important to have in mind that this is not an exact measure, rather a rough estimate of a lifetime AAS dose.

3.5 Previous or current drug problem

The presence of a previous or current drug problem was determined based on some fixed guidelines and partly by discretionary evaluation. The following information was used; two scales from the MCMI-III; the drug and the alcohol dependence scales, self-reports on previously used substances outside medical use (e.g. ecstasy, cocaine, MDMA, Paralgin Forte). This form was taken from the M.I.N.I.-plus psychiatric diagnostic interview instrument (version 5.0; Sheehan et al., 1998). Further information was based upon reports about number of times used alcohol and illicit drugs the last six months on obtained from the ASEBA Adult Self-Reports (ASR) questionnaire.

Of these measures the two MCMI scales were given the most weight in the assessment. Participants that obtained a base rate (BR) score of 75 or above (indicating the presence of a clinical syndrome) on one of these scaled fulfilled the criteria of having a "previous or current drug issue". If participants obtained BR scores close to 75 (> 70), then the evaluation was guided by the self-report and the ASR information.

The self-report schema was Taken from the M.I.N.I.-plus psychiatric diagnostic interview instrument (version 5.0), (evaluating substance dependence), and was administered during the interview. Participants were asked to mark substances they have ever used in order to get high, followed-up by questions to clarify whether the reported substances had been

used extensively or only a few times, to get an indication of the duration of use, and if the substances in question were still being used by the participant or not.
Borderline cases were discussed by two investigators, and often a strict evaluation was preferred as it was considered to be valuable to be able to conduct analyses where concurred substance abuse would have minimal influence on the findings.

3.6 Executive functions

Executive functions were assessed using the Color Word Interference Test (CWIT) and Trail Making Test (TMT) from the D-Kefs battery (Delis, Kaplan & Kramer, 2001), as well as the Attention Network Test (ANT, Fan et al., 2002).

In the CWIT the participant is presented with a paper sheet on which the stimuli are printed. It consists of four conditions: In the first condition, the sheet consists of colored patches (red, green and blue) and the participant is instructed to say out loud the colors of the patches. The second condition involves reading color words (red, green and blue) written in black ink. In the interference condition, color words are presented written in ink of another color (either red, green or blue). The participant is instructed to say out loud the color of the ink, and override the impulse to read the word. This then, tests the participant's ability to override an impulse (reading the word) to complete the task successfully, and was used as a measure of executive inhibition. Lastly, the fourth condition again involves color words written in colored ink, with some of the words printed inside rectangles. The participant is given the same instructions as in the third condition, with the added rule that the participant is to read the words placed in rectangles, regardless of the color of the ink. This test requires the ability to shift between different rules, and is thus a measure of cognitive flexibility. In all conditions, the participant is instructed to complete the task as fast as they can without making any errors. In addition to time taken to finish the third and fourth conditions, the total number of errors committed on these conditions was also included as a measure of inhibition (MacLeod, 1991). Errors were recorded when the participant read the word instead of saying the color in the third condition, and when the participant read the words outside rectangles or said the color of the word inside rectangles on the fourth condition. Errors were recorded whether or not the participant immediately corrected the error. Contrast measures were obtained by subtracting the scores on CWIT 1 and 2 from the results on CWIT 3, in order to remove the effect of processing speed on this measure (Delis, Kaplan & Kramer, 2001). This created two new variables of inhibition; $CWIT_{3\text{-}1}$ and $CWIT_{3\text{-}2}$. Subtracting the scores on

CWIT 3 from scores on CWIT 4 created a measure of cognitive flexibility removing the effect of processing speed and inhibition: $CWIT_{4-3}$.

Like the CWIT, the TMT has four conditions and is a pencil and paper test. In the first condition, numbers and letters are presented in a scrambled fashion on the paper. The participant is tasked with finding and crossing out all 3s. This test involves visual search and psychomotor speed. In the second condition, the participant is similarly presented with numbers and letters but asked to draw a line from number to number in a rising order, from 1 to 16. The third condition is similar, other than the participant being tasked with drawing a line from letter to letter in alphabetical order. This are tests of psychomotoric speed. On the fourth condition the participant is instructed to draw a line like in the previous two conditions, but this time the line is to be drawn alternating between number and letter (1-a-2-b etc.). This is a measure of cognitive flexibility as it involves shifting attention as well as cognitive rules. Contrast measures were obtained in a similar fashion as for the CWIT; by subtracting the scores on TMT 3 and 2 from the scores on TMT 4 in order to remove the effect of psychomotoric speed on this measure, creating two new variables: TMT_{4-2} and TMT_{4-3}.

Another measure of executive functioning was the conflict-condition on the Attention Network Test (ANT, Fan et al., 2002). The ANT is a reaction time test designed to measure three aspects of attention: Alerting; maintained vigilant attention, Orienting; selection of and orienting toward sensory information and Executive control; the process of resolving incongruent stimuli (Westlye et al., 2011). In the ANT, the participant is asked to fixate on a contrally located cross on a computer screen. The stimuli consist of five arrows presented either immediately above or immediately below the fixation point. The participant's task is to indicate whether the middle arrow points to the left or to the right by pressing one of two buttons. The stimuli may be congruent; all the arrows point in the same direction, or incongruent; the flanking arrows point in the opposite direction of the middle arrow. The conflict measure is computed by subtracting the median reaction time (RT) for congruent stimuli from the median RT for incongruent stimuli, and then dividing the difference by the median RT of the congruent stimuli. This score is a measure of executive control, as it pertains to the ability to resolve cognitively incongruent stimuli and disregarding distracting stimuli (Westlye et al., 2011).

3.7 Aggression

Aggression was assessed using the Buss Perry Aggression Questionnaire (BPAQ, Buss & Perry, 1992). This is a 29-item questionnaire that produces four subscales and an additional total aggression scale. The subscales are ”physical aggression”, ”verbal aggression”, ”anger” and ”hostility”, as well as ”total aggression”; the sum of the scores on the four subscales. These four factors have been replicated through factor analysis in several languages (Vigil-Colet et al., 2005). The physical and verbal aggression subscales represent the behavioral manifestations of aggression in the BPAQ, in that they assess the degree to which the participant tends to use or is willing to use aggressive behavior within the physical or verbal domain. The anger subscale assesses the participant's physiological arousal and preparedness to experience aggression (Buss & Perry, 1992). Anger has been conceptualized as a trait, and defined as "the disposition to perceive a wide range of situations as annoying or frustrating and by the tendency to respond to such situations with elevations in state anger" (Spielberger, 1999, cited in Owen, 2011). The hostility scale assesses the participant's feelings and thoughts of rancor and malice, thus pertaining to cognitions regarding aggression (Buss & Perry, 1992).

3.8 Pattern of use

In addition to the estimated lifetime dose and AAS-dependency, total number of years used and debut age were used as measures of pattern of AAS use, based on self-reports. The calculation of estimated lifetime dose is detailed above. Debut age was recorded as the participant's age at first exposure to AAS. Total number of accumulated years used is the total number of years the participant considered himself an AAS user, including periods between AAS cycles. Participants were categorized into one of three groups regarding total years of cumulative use; Short- (1-4.99 years, N=19), medium- (5-9.99 years, N=34) and long- (≥10 years, N=34) term use. Note that "long-term" is here used in a relative fashion, as all participants in the AAS sample could be described as having a long-term AAS career (more than one year).

3.9 Statistical analyses

All analyses were performed using SPSS version 22. Assumptions were checked before using parametric tests in analyses. Normality was checked using Shapiro-Wilk Test and

Kolmogorov-Smirnov Test. Considering the present investigations rather large sample size, we also checked distributions using histograms on variables whose tests of non-normality were significant (Field, 2009). Assumptions about homogeneity of variance were assessed using Levene's Test for homogeneity of variance. Missing values for questionnaire variables were replaced by predicted values using the expectation-maximization method (Howell, 2007) after checking the assumption that they were missing in a random order, using Little's Missing Completely At Random-test (Little's MCAR test; Little, 1998).

Main effects of group on BPAQ-scores were first tested using general linear modeling, with group as fixed factor and age as covariate. The same analyses were used when testing main effects on neuropsychological test scores, also including education level as a covariate, as these are known correlates across a range of cognitive functions (Lezak et al., 2012). For the ANT scores, no covariates were included, as these were T-scores. The variables of errors committed on CWIT 3 and 4 were heavily skewed toward few or no errors. Group differences on this measurement will thus be analyzed using Mann-Whitney's U test. These analyses did not include age as a covariate, as there age effects on number of errors committed on the CWIT are small in the age group under investigation here (Delis, Kaplan & Kramer, 2001). On all measures of executive functioning, we did separate analyses for a subsample of participants with and without previous or current drug problem, as use of a range of illicit substances is a known risk factor for impaired cognitive functioning (Lezak et al., 2012). Differences on important demographic variables were assessed using Student's T-test, and when assumptions about normality did not hold, Mann-Whitney U. In the latter case, effect sizes were calculated by hand (see Field, 2009).

Correlations between AAS age of onset, estimated lifetime dose and BPAQ-scores were tested using Partial Correlation, controlling for age. In case of neuropsychological test data, education level was controlled for in addition to age. In cases were assumptions about normality were not fulfilled, correlations were assessed using Spearman's Rho. As non-parametric partial correlation is not a default option in SPSS, this was achieved using an edited syntax that used results from correlation analysis using Spearman's Rho as basis for a new partial correlation (IBM, 2015; see appendix 3).

Exploratory analyses were then performed to assess further the associations between AAS use pattern and aggression and executive functions.

4 Results

4.1 Descriptive statistics

Descriptive statistics concerning age, education level and exercise habits are presented in table 1. The groups did not differ significantly in age, as controls had a mean age of 31.8 (SD=9.4) years while users had a mean age of 33.4 (SD=8.4). Controls had a mean of 15.8 (SD=2.7) years of education while users had a mean of 14.2 (SD=2.7), which was a significant difference ($T=3.56$, $p<.01$). The groups were similar on all measure of exercise habits, except time spent strength exercising where controls spent significantly more time per week ($t=2.96$, $p<.05$). Controls spent 463 (SD=242) minutes per week while AAS users spent 351 (SD=204) minutes strength exercising. AAS users reported significantly higher personal records on bench press (M_{con}=138.5 kg, M_{AAS}=168.4 kg, $t=-6.29$, $p<.001$), squat (M_{con}=172.9 kg, M_{AAS}=216.4 kg, $t=-4.98$, $p<.001$) and deadlift (M_{con}=199.6 kg, M_{AAS}=216.4 kg, $t=-3.80$, $p<.001$).

Controls reported consuming a mean of 3.25 (SD=4.75) units of alcohol per week, while users reported a mean of 1.63 (SD=3.12) units per week, which was a significant difference ($t=2.53$, $p<.05$). A total of 64 (92.8%) of controls were classified as not having a previous or current drug problem, while 4 (5.8%) were. In the user group, 52 (59.1%) were classified as not having a previous or current drug use, while 35 (39.8%) were. A Chi-square test revealed a significant association between group and being classified as having a previous or current drug problem (X^2 (df=1, N=155) = 23.91, $p<.01$), with significantly more users being classified as having a previous or current drug problem. Accordingly, this will be taken into account in the statistical analysis concerning aggression and executive functions.

Concerning the nature of AAS use in the user group, 30 (34.5%) of the users reported having ceased using AAS, while 54 (62.1%) reported to still be active AAS users. Mean debut age of AAS use was 22.14 (6.54) years, ranging from 12 to 52 years. The mean estimated lifetime dosage was 368 364.40 (SD=523 510.15) mg, ranging from 15000.00 mg to 3 969 375.00 mg. The mean number of total years of AAS use was 9.13 (5.68) years, ranging from 1 to 30 years.

4.2 Executive functions

4.2.1 Cognitive flexibility

On the CWIT 4 controls used on average 55.9 (SD=12.7) seconds to finish the fourth condition on the CWIT 4 task, while users required on average 63.7 (SD=19.1) seconds to finish. This difference tended toward significance ($F(1,150)=3.06$, $p=.08$). On the TMT 4, controls used on average 66.3 (SD=20.1) seconds while AAS users used 81.4 (SD=30.4) seconds. This difference was significant ($F(1,150)=6.77$, $p<.05$) with a small effect size ($\eta^2=.04$). Concerning the contrast measures, controls and AAS users did not differ on the $CWIT_{4-3}$ ($M_{con}=4.01$ (10.01), $M_{AAS}=4.94$ (15.97), $F(1,136)=.26$, $p=.61$). Neither did they differ on the TMT_{4-2} ($M_{con}=40.52$ (19.67), $M_{AAS}=48.97$ (27.79), $F(1,136)=1.92$, $p=.17$) or the TMT_{4-3} ($M_{con}=39.56$ (20.46), $M_{AAS}=47.97$ (26.86), $F(1,136)=1.92$, $p=.17$).

Further analyses including a subsample of only controls (N=64) and users (N=50) without a previous or current drug problem, a significant difference was found on the TMT 4 ($M_{con}=66.92$, $M_{AAS}=80.57$, $F(1,110)=5.75$, $p<.05$) with a small effect size ($\eta^2=.05$). The difference between controls and AAS users in this subsample was not significant for the CWIT 4 ($M_{con}=55.72$ (12.92) seconds, $M_{AAS}=63.08$ (18.81), $F(1,110)=1.77$, $p=.19$). These groups did not differ significantly on either of the contrast measures of cognitive flexibility.

4.2.2 Inhibitory control

Controls used on average 52.1 (SD=11.8) seconds while AAS users used on average 58.4 (SD=15.8) seconds to finish CWIT 3. This difference was statistically significant ($F(1,150)=4.45$, $p<.05$) with a small effect size ($\eta^2=.03$). On CWIT 3, controls committed on average 0.80 errors while users committed on average 1.25 errors. This difference was significant ($z=-2.31$, $p<.05$) with a small effect size ($r=.19$). On CWIT 4, controls committed on average 1.1 (SD=1.6) errors, while users committed 1.8 (SD=2.0), resulting in a significant difference ($z=-3.20$, $p<.01$) with a medium effect size ($r=.26$). The groups did not differ significantly on the contrast measures, but these differences tended toward significance: $CWIT_{3-1}$ ($M_{con}=21.97$ (8.83), $M_{AAS}=26.12$ (13.43), $F(1,148)=2.73$, $p=.10$); $CWIT_{3-2}$ ($M_{con}=30.61$ (10.01), $M_{AAS}=35.40$ (14.45), $F(1,148)=3.21$, $p=.07$).

When investigating a subsample consisting of only controls (N=64) and users (N=50) without a previous or current drug problem, the groups still differed significantly on CWIT 3 ($M_{con}=51.53$ (10.39) seconds, $M_{AAS}=58.14$ (15.34) seconds, $F(1,110)=4.42$, $p<.05$) with a

small effect size (η^2=.04). These groups also differed on the contrast measures $CWIT_{3-1}$ (M_{con}=21.31 (6.99), M_{AAS}=25.94 (12.49), F(1,110)=4.34, p<.05, η^2=.04) and $CWIT_{3-2}$ (M_{con}=30.10 (8.33), M_{AAS}=35.27 (13.06), F(1,110)=4.41, p<.05, η^2=.04) (see fig. 1). Controls in this subsample also displayed significantly fewer errors committed on CWIT 3 (M_{con}=.73 (SD=1.06) errors, M_{AAS}=1.18 (SD=1.19) errors, z=-2.26, p<.05) and CWIT 4 (M_{con}=1.13 (SD=1.59) errors, M_{AAS}=1.88 (SD=2.17) errors, z=-2.38, p<.05), with medium effect sizes (CWIT 3 errors: r=.21; CWIT 4 errors: r=.22).

4.2.3 Executive control

On the conflict condition of the ANT, controls acquired a mean T-score of 8.81 (SD=2.57) while users had a mean T-score of 7.64 (SD=2.69). This difference was significant (F(1,147)=7.31, p<.001) with a small effect size (η^2=.05). Mean scores for these groups are presented in fig. 2.

When investigating a subsample consisting of only controls (N=64) and users (N=50) without a previous or current drug problem, a significant difference still emerged on the Conflict-condition of the ANT (M_{con}=8.84 (SD=2.49), M_{AAS}=7.67 (SD=2.36), F(1,110)=6.40, p<.05) with a small effect size (η^2=.06).

4.2.4 Pattern of use

When comparing a subsample of AAS users with 10 or more years of total AAS use (N=33) to controls (N=69), significant differences still emerged on the $CWIT_{3-1}$ (M_{con}=21.97 (8.83), M_{AAS}=28.67 (16.80), F(1,98)=4.10, p<.05, η^2=.04) and $CWIT_{3-2}$ (M_{con} =30.61 (10.01), M_{AAS}=38.89 (16.94), F(1,98)=6.76, p<.05, η^2=.06). Both effect sizes were small. Scores on these measures were not related to any other measures of pattern of use.

4.2.5 Self-reported side effects

A total of 16 (18.8 %) of AAS users included in analyses of executive functions reported experiencing either “being impulsive” or “poorer impulse control” as a side effect of AAS use. Further, 3 (3.5 %) AAS users reported problems with concentration associated with AAS use. Thus, 19 (22.3 %) of AAS users reported side effects that may be related to executive functions.

4.3 Aggression

4.3.1 Group differences

There were significant group differences on the total aggression scale and nearly all subscales of the BPAQ. These results are presented in table 2 and fig. 3. On the Total Aggression Scale, controls acquired a mean score of 73.11 (SD=19.85) compared to 97.28 (SD=30.11) in the user group. This was a significant difference ($F(1,133) = 31.24$, $p<.001$) with a strong effect size (η^2=.19). Following are the mean scores on the subscales for controls and AAS users respectively: 21.80 (SD=8.64) versus 33.57 (SD=12.82) on physical aggression ($F(1,133) = 39.62$, $p<.001$, η^2=.23); 18.40 (SD=5.48) versus 20.12 (SD=6.34) on Verbal aggression, a significance which only tended toward significance ($F(1,133)=3.34$, $p=.07$); 15.77 (SD=6.35) versus 22.00 (SD=9.50) on Anger ($F(1,133) = 20.25$, $p<.001$, η^2=.13); and 17.14 (SD=7.47) versus 21.59 (SD=9.05) on Hostility ($F(1,133) = 10.06$, $p<.01$, η^2=.07). Effect sizes ranged from small (Hostility) to moderate (anger) and strong (Total Aggression, Physical Aggression)

When comparing AAS users that had ceased using and active users, statistically significant differences emerged on the anger, hostility and total aggression scales of the BPAQ: Anger (M_{ceased}=25.35, M_{active}=20.20, $F(1,68)=4.61$, $p<.05$, η^2=.06), hostility (M_{ceased}=25.05, M_{active}=19.67, $F(1,68)=5.99$, $p<.05$, η^2=.08), and total aggression (M_{ceased}=106.76, M_{active}=91.95, $F(1,68)=3.84$, $p<.05$, η^2=.05). All these effect sizes were small.

4.3.2 Aggression in AAS users without concurrent drug use

When excluding participants with a current or previous drug problem, the remaining subsample of AAS users (N=44) still displayed higher scores than controls (N=58). Following are the mean scores for controls and users respectively for the subscales: 21.11 (SD=8.08) versus 30.08 (SD=11.85) on physical aggression ($F(1,99) = 21.13$, $p<.001$, η^2=,18); 18.26 (SD=5.56) versus 19.34 (SD=6.28) on verbal aggression ($F(1,99)=1.13$, $p=.291$); 15.47 (SD=6.39) versus 19.52 (SD=8.45) on Anger ($F(1,99) = 7.86$, $p<.01$, η^2=.07); 16.74

(SD=6.90) versus 19.78 (SD=7.56) on Hostility (F(1,99) = 4.69, p<.05, η^2=.05); and 71.58 (SD=18.21) versus 88.72 (SD=27.95) on Total Aggression (F(1,99) = 14.80, p<.001, η^2 =.13). Thus, when comparing controls and AAS users without a previous or current drug problem, there were still significant main effects of group and small (Anger, Hostility) to medium (Physical Aggression, Total Aggression) effect sizes on all subscales of the BPAQ, except the Verbal Aggression subscale.

When comparing AAS users without a previous or current drug problem (N=44) to AAS users with (N=29), significant differences emerged on the Total Aggression scale and all subscales, except Verbal Aggression. Means and SDs for this subsample are presented in table 3. For Total Aggression AAS users without a previous or current drug problem obtained a mean score of 88.72 (SD=27.95) versus 110.27 (SD=29.00) for users with a previous or current drug problem, a significant difference (F(1,70)=9.84, p<.01, η^2=.12). Following are mean scores on the subscales for AAS users without and with a previous or current drug problem respectively: 30.08 (SD=11.85) versus 38.86 (SD=12.60) on Physical Aggression (F(1,70)=8.89, p<.01, η^2=.11); 19.34 (SD=6.28) versus 21.31 (SD=6.35) on Verbal Aggression (F(1,70)=1.61, p=.21); 19.52 (SD=8.45) versus 25.75 (SD=9.90) on Anger (F(1,70)=8.07, p<.01, η^2=.10); and lastly 19.78 (SD=7.56) versus 24.34 (SD=10.49) on Hostility (F(1,70)=4.56, p<.05, η^2=.06). In these comparisons effect sizes were small (Hostility) to moderate (Physical Aggression, Anger and Total Aggression). Mean scores for controls, AAS users without and AAS users with a previous or current drug problem are presented in fig. 4.

3.3.3 Pattern of AAS use:

Using Spearman's Rho, controlling for age, estimated lifetime dose correlated significantly with the physical aggression subscale (N=67, r=.28, p<.05), the anger subscale (r=.38, p<.01) and the total aggression scale (r=.32, p<.01). The correlations were all positive, indicating that a higher estimated lifetime dose was associated with higher scores on different aggression scales. The relationship between estimated lifetime dose and scores on the Physical Aggression subscale is presented in a scatter plot in fig. 5.

Considering total duration of AAS use in relation to aggression measures, there were significant differences between short- (N=15), medium- (N=29) and long-term (N=29) AAS

users. Anger (F(2,69) = 5.12, p<.01, η^2=0.13), Hostility (F(2,69) = 7.75, p<.01, η^2=.18) and Total Aggression (F(2,69) = 4.61, p<.05, η^2=.12) showed a significant main effect of use duration. This effect was not significant for Physical Aggression (F(2,69)=1.94, p=.15). Mean scores for the duration groups and controls are shown in Fig. 6.

AAS users that fulfilled the SCID-criteria of an AAS dependency syndrome scored higher on the BPAQ compared to AAS users that did not fulfill these criteria. A main effect of AAS dependency was found on several subscales of the BPAQ. Following are the mean scores for non-dependent and dependent AAS users respectively: 28.85 (SD=11.60) versus 37.92 (SD=12.47) on Physical Aggression (F(1,70)=9.71, p<.01, η^2=.12); 18.46 (SD=9.08) versus 25.26 (SD=8.76) on Anger (F(1,70)=9.95, p<.01, η^2=.12); 19.06 (SD=7.10) versus 23.92 (SD=10.07) on Hostility (F(1,70)=5.39, p<.05, η^2=.07); and 85.28 (SD=25.96) versus 108.34 (SD=29.71) on Total Aggression (F(1,70)=11.68, p<.01, η^2=.14).

4.3.4 Age of onset

In correlational analyses involving age of AAS onset, we used Spearman's Rho controlling for age, as the age of onset-variable was highly leptokurtic and skewed toward adolescence. These analyses included 70 AAS users. Age of onset of AAS use was negatively correlated with two subscales, as well as the total aggression scale on the BPAQ: Physical Aggression (r_s=-.28, p<.05), Anger (r_s=-.28, p<.05) and Total Aggression (r_s=-.29, p<.05). All of these correlations were weak. Negative correlations indicate that a higher debut age was associated with lower scores on the Physical aggression and Anger subscales, as well as the Total aggression scale.

4.3.5 Self-reported side effects

Of the 73 AAS users who turned in their BPAQ, a total of 31 (42.5 %) reported experiencing "aggression" as a side effect of AAS use. An additional 6 (8.2 %) users reported "short fuse", 6 (8.2 %) users reported "irritability" and 5 (6.8 %) reported "mood swings" without mentioning aggression. Thus, a total of 48 (65.8 %) of the AAS users reported aggression or mood related side effects (see fig. 7).

4.6 Aggression and Executive functions

Inhibition, as measured by the contrast measures of the CWIT, correlated significantly with the Total Aggression Scale of the BPAQ: $CWIT_{3\text{-}1}$ ($r=.17$, $p<.05$); $CWIT_{3\text{-}2}$ ($r=17$, $p<.05$). The contrast measure of the CWIT did not correlate significantly with any of the subscales, however. No other measures of executive functions correlated with measures of aggression.

5 Discussion

The principal findings from the present investigation were that AAS users performed worse than non-AAS using controls on measures of executive inhibition and executive control, and that AAS users achieved higher scores than controls on self-report measures of aggression. Furthermore, higher levels of aggression were associated with a combination of AAS and a previous or current drug problem, fulfilling the criteria for AAS dependency, having a longer duration of AAS use, higher estimated lifetime dosages and lower age of onset.

As in numerous previous studies, the sample in this investigation presented with a significantly higher prevalence of drug abuse among AAS users. The reasons behind the high prevalence of concomitant drug use in AAS users have been hotly debated. A general pattern of risk-taking behavior thought to predispose individuals to both experimenting with AAS and other drugs of abuse has been proposed as one explanation (Pallesen et al., 2006; Williamson & Young, 1992). Some evidence also indicates that AAS might lead to neurochemical alterations that can predispose AAS users to use of other illicit drugs of abuse. Rats treated with AAS (nandrolone) self-administer significantly more alcohol than vehicle treated rats (Johansson et al., 2000). Indeed, there is a growing literature on the effects of AAS on the opioid system, indicating that use of AAS may alter this system to increase vulnerability for opioid dependence in AAS users (Nyberg & Hallberg, 2012). The lower levels of inhibition and executive control displayed by AAS users in the present investigation may also provide one other mechanism behind this association as low inhibition has been shown to be a risk factor for abuse of a range of recreational drugs (Jentsch & Pennington, 2014). This may increase the prevalence of use of other illegal substances either through a common predisposing factor or a negative side effect induced by AAS use, or both.

5.1 Executive functions

The finding that AAS users report higher levels of aggression than controls was expected on account of the abundance of research on this association. However, this is to the best of our knowledge the first time that long-term use of AAS in humans has been associated with lower levels of executive inhibition and executive control compared to non-AAS using controls. We have found in a large sample of previous and current AAS users without a history of drug abuse, that long-term AAS use is associated with lower levels of executive inhibition and executive control. This finding confirmed our hypothesis that AAS users would display lower

levels of executive functions compared to controls. It also supports the few animal studies on AAS use and executive functions in rats, which have found AAS to lead to alterations in the prefrontal cortical-striatal circuitry important for executive functions (Wood et al., 2013).

Findings on executive functions were not uniform however. When including the entire sample, AAS users performed significantly worse than controls on executive control. Concerning executive inhibition, AAS users performed significantly more errors on the third and fourth conditions of the CWIT, but the contrast measures only tended toward significance. Self-reports concerning side effects of AAS use also support the finding that AAS users perform somewhat poorer on measures of inhibition, as 16 (18.8 %) of AAS users reported diminished impulse control as a negative side effect of AAS use. While a main effect of group appeared on the TMT 4, the contrast measures of TMT_{4-3} and TMT_{4-2} did not reveal significant differences between AAS users and controls. Thus, the significant difference on the TMT 4 likely reflects a poorer psychomotoric speed in AAS users compared to controls rather than an impaired capacity for cognitive flexibility. The contrast measure $CWIT_{4-3}$ also revealed no difference between controls and AAS users.

As noted, many AAS users had a previous or current drug problem. Abuse of a range of psychostimulants has been associated with impairments in several cognitive domains (Wood et al., 2014). Cocaine, for example, has been associated with impairments in psychomotoric speed (Beatty et al., 1995) and executive functions (Beveridge et al., 2008; Kalapatapu et al., 2011). A similar pattern has been shown for amphetamine (Scott et al., 2007). The high prevalence of use of such illicit drugs of abuse in the user group warranted separate analyses and considerations for AAS users without use of these other substances. When conducting separate analyses for AAS users without a previous or current drug problem, a somewhat different pattern emerged for neuropsychological test results of executive functions.

Concerning executive inhibition, controls and AAS users without a previous or current drug problem differed significantly on the $CWIT_{3-1}$ and $CWIT_{3-2}$, with these AAS users performing significantly worse than controls. Users in this subsample also made significantly more errors on both CWIT 3 and 4. Thus, AAS users with no history of drug abuse performed worse than controls on all four measures of executive inhibition. The conflict condition of the ANT also revealed a significant difference between AAS users and controls, with controls achieving significantly higher T-scores. These findings indicate that AAS users have a lower

capacity to override impulses by using top-down executive functions and are slower at resolving conflicting stimuli compared to non-AAS using controls.

One somewhat unexpected finding was that the difference between AAS users and controls on the contrast measures of inhibition only tended toward significance when including participants with a previous or current drug problem. This may be explained by the inclusion of controls with a previous or current drug problem (N=4), who obtained significantly worse mean scores than controls and both groups of AAS users on the two contrast measures on inhibition. AAS users with a history of drug abuse performed no different than AAS users without (see fig. 8).

Controls and AAS users did not differ on any measure of cognitive flexibility. This somewhat contradicts the finding from one study that found decreased levels of behavioral flexibility in rats treated with AAS (Wallin & Wood, 2015). The cause behind this discrepancy may stem from the way flexibility was assessed. The CWIT 4 and TMT4 assess relatively restricted subcomponents of flexibility: The CWIT 4 assesses flexibility by requiring the participant to shift cognitive rule sets, while the TMT4 assesses flexibility by requiring the participant to shift back and forth between two different classes of stimuli, and is important for higher level tasks such as multi-tasking and divided attention (Delis, Kaplan & Kramer, 2001). Wallin and Wood (2015) used a rule-reversal paradigm, requiring the participant to "unlearn" learned rules to continue succeeding in a task. This could be conceptualized as a more global test of flexibility, comparable to the Wisconsin Card Sorting Test (Lezak et al., 2012) in humans, which was not included in the present study.

The lower levels of executive inhibition and executive control seen in AAS users may be attributed to a neurotoxic effect of AAS. As has been described earlier, AAS has been shown to lead to alterations in dopamine functioning in the prefrontal cortical-striatal circuitry (Wood et al., 2013; Kurling-Kailanto, Kankaanpää & Seppälä, 2010) and alterations in brain nerve growth factor in the basal forebrain of rats (Pieretti et al., 2012). The prefrontal cortical-striatal circuitry is important for executive functions, such as behavioral flexibility (Wallin & Wood, 2015) and risk-reward decision making (Simon et al., 2011). The finding that AAS users without a previous or current drug problem performed worse than controls on measures of executive inhibition and executive control, and the findings from animal models, indicates that the lower levels of executive inhibition and executive control in the AAS users may not be attributable to the high prevalence of concomitant drug use in this group.

Aside from the possibly neurotoxic effect of AAS, another explanation behind the lower scores of executive functions in AAS users is that lower levels of executive functioning might be a risk factor for AAS use. While this possibility has not been explicitly investigated for AAS use, poor inhibition and impulsiveness has been identified as a risk factor for use of a range of other illicit substances (Jentsch & Pennington, 2014). For example, longitudinal studies have shown poor inhibition in childhood to be related to a higher risk for alcohol dependency and use of illicit substances later in life (Caspi et al., 1996; Tarter et al., 2003). Hypothetically, individuals with a lower level of inhibition initially, might be more prone to yield to the tempting fast route offered by AAS and less capable at ceasing AAS use in face of negative side effects. Lower executive functioning prior to AAS use would lend support to the risk taking behavior-hypothesis, which has been put forward as one explanation of the high prevalence of concurrent drug use in AAS users (van Amsterdam, Opperhuizen & Hartgens, 2011).

In addition to a direct causal neurotoxic effect and lower executive functions as a risk factor for AAS use, some of the medical conditions associated with AAS use can be thought to impact executive functions. AAS use has been associated with a multitude of medical conditions (Golestani et al., 2011). Several studies have found increased prevalence of hypertension in AAS users compared to controls in the absence of other known risk factors (Hartgens & Kuipers, 2004; Achar et al. 2010; van Amsterdam, Opperhuizen & Hartgens, 2011; but see Edvardsson, 2014). Hypertension is of course a risk factor for cognitive impairment through the significantly elevated risk for vascular accidents (Lezak et al., 2012), but in the current study, these such participants would be excluded. Hypertension unrelated to stroke is on the other hand an established risk factor for cognitive impairment, possibly through increased occurrence of covert vascular brain injury (Tzourio, Laurent & Debette, 2014). Across cognitive domains, especially executive functions and processing speed have been shown to be more susceptible to decline due to hypertension than other cognitive abilities (Debette et al., 2011). As we did not collect data on the AAS users' blood pressure, this is a possibility that deserves further investigation.

Recurrent periods of hypogonadism after AAS cycles may also constitute a risk factor for cognitive decline. Hypogonadism has been associated with lowered levels of cognitive functioning in old men (Beauchet, 2006) and patients following traumatic brain injury (Wagner et al., 2012). Testosterone binds to the androgen receptors, which are widely distributed throughout the brain (Cherrier, 2009), and one might hypothesize that the tides of

exogenous androgens and aromatized estrogens that flood and drain these areas within and between cycles may be a possible mechanism behind cognitive decline in long-term AAS users.

We thus have three probable mechanisms behind the lower scores on measures of executive functions in AAS users: (1) A neurotoxic effect of AAS, (2) poorer inhibition prior to debut as a risk factor for AAS use and (3) through a variety of medical conditions associated with AAS use, such as hypertension and hypogonadism. These hypotheses are not mutually exclusive, of course. They may all be true, so that individuals with a lower baseline executive functioning may experience a further decline as a consequence of long-term AAS use. A similar pattern has been observed in individuals with addiction to other illicit substances, with a low inhibition initially exacerbated by drug use (Jentsch & Pennington, 2014). The finding that AAS users without a history of drug use still performed worse than controls may lend support to the hypothesis that AAS has a neurotoxic effect on the human brain, leading to lower levels of executive control and executive inhibition. While a smaller sample (N=33) of AAS users with a very long use duration (10 years or more) still displayed lower levels of inhibition than controls may lend support to the notion that use duration can influence level of executive inhibition in AAS users, levels of executive functioning were not related to any other measure of usage pattern. However, while we failed to find a dose-dependent relationship between AAS use and cognitive symptoms, such a relationship was reported in the study by Kanayama and colleagues (2013).

While poorer executive functions as a risk factor for AAS use may be one of the explanations behind this finding, one factor may have led us to underestimate this effect. The group of long-term AAS users is heterogeneous. While use of AAS has consistently been associated with use of other illicit substances and criminality, many AAS users do not engage in any of these behaviors. The study of 1,955 AAS users by Cohen and colleagues (2007) concluded that the average AAS user is highly educated, earns an above average wage and is motivated by the desire for increased physical strength and attractiveness. A majority of these users reported following strict dietary plans, and planning their AAS cycles minutely. These patterns of use would conceivably require higher levels of executive functions, such as inhibition in order to stick to these dietary regimens. As such, these individuals could be thought to have a high level of executive functioning initially that would limit our finding of AAS induced effects on executive inhibition and control. We did not identify AAS users belonging to this group in our study. Additionally, many of the users in our sample reported

following strict plans and to use AAS in a goal-directed fashion, while others did not. This may be one of the explanations behind the relatively weak effects of AAS on executive inhibition seen in the present sample.

While this investigation showed AAS users to perform worse than controls on several measures of executive inhibition and executive control, the choice of control group might not be the most appropriate for this kind of comparison. Our control group consisted of recreational sportspeople who frequently lift weights. Physical exercise has previously been shown to improve cognition and executive functions in normal populations (Guiney & Machado, 2012; Colcombe & Kramer, 2003). Animal models have linked exercise with increased neurogenesis in the dentate gyrus of rodents (Farmer et al. 2004, Praag, Kempermann & Gage, 1999), providing a possible mechanism for the improvements in cognition and executive functions seen in exercisers. AAS have been shown to suppress neurogenesis in the dentate gyrus (Brännvall et al., 2005), as well as ameliorate the positive effects of strength exercise on cognition trough suppression of this effect (Novaes Gomes et al., 2014). One possibility is that AAS users in the present sample only performed worse than controls because the control group had the positive effect of exercise on executive functions. If this is true, AAS users would not have poorer executive functioning compared to non-AAS using individuals without the positive effect of exercise on cognition and executive functions. However, AAS has not only been related to the amelioration of positive effects of exercise on executive functions. As mentioned above, AAS use has been associated with neurochemical alterations in the prefrontal cortical-striatal circuitry (Wood et al., 2013; Wallin & Wood, 2015) and brain nerve growth factor (Pieretti et al., 2012), indicating that AAS may have a debilitating effect on brain areas important for executive functions, beyond mitigating the positive effects of exercise. In addition to this, the study by Brännvall and colleagues (2005) found a decrease in neurogenesis in the dentate gyrus of AAS users compared to non-exercising controls, indicating that this effect goes beyond the removal of the positive effects of physical exercise.

Taken together, the findings of the present study indicate that AAS users without a history of drug use perform worse than non-AAS using controls on measures of executive inhibition and executive control, thus confirming our hypothesis that AAS use is associated with lower levels of executive functions. The findings were strongest for executive control, followed by executive inhibition, with significant differences on the conflict measure of the ANT and all four measures of inhibition. In contrast to this, AAS users did not perform worse

than controls on measures of executive flexibility. The differences in executive functions may be explained by AAS use directly, through a neurotoxic effect, or indirectly, through related medical conditions. Alternatively, it may be explained by lower executive functioning in AAS users prior to AAS use, or by a combination of these pathways. Measures of executive functions were not associated with severity of AAS use, leading to a rejection of the hypothesis that levels of executive functioning were associated with aspects of AAS pattern of use. Further research is clearly needed to assess the degree to which impaired executive functions is a risk factor for AAS use and elucidate the possibly causal links between AAS use and lowered executive functions in humans.

5.2 Aggression

The other main finding from this investigation was that AAS users displayed significantly higher levels of physical aggression, anger and hostility on self-report measures. This corroborates the findings of numerous previous investigations into AAS and aggression (e. g. Su et al., 1993; Trenton & Currier, 2005; Pagonis et al., 2006a). Furthermore, aggression levels were related to several measures of pattern of use. These findings confirmed the hypotheses that AAS users would show higher levels of aggression and that these levels would be associated with a more severe pattern of use.

One of the most salient and strong findings was the large difference between AAS users and controls on the measure of physical aggression. This finding also aligns well with previous findings from both animal studies (e. g. Salas-Ramirez, Montalto & Sisk, 2010) and human studies that have found AAS to be particularly characteristic of perpetrators of violent crimes (e. g. Beaver, Vaughn & Wright, 2008) and violent behaviors (e. g. Pope & Katz, 1990; Trenton & Currier, 2005). These findings are especially troubling considering how physical violence can have far reaching consequences for the person it targets and the perpetrators of violence themselves, as well as substantial societal costs associated with violence (WHO, 2014). Physical aggression scores were positively correlated with estimated lifetime dose of AAS, indicating that a higher lifetime consumption of AAS substances is associated with higher levels of physical aggression. Furthermore, users with medium-term AAS use (5-10 years) achieved higher scores than users with short-term (1-5 years) use, while users with long-term AAS use (10+ years) achieved slightly lower scores than the medium term group (see fig.6). This may be a result of measurement error; however it may also be

explained by the relatively higher age of this group, as frequency and severity of physical aggression decrease with age (Sweeten, Piquero & Steinberg, 2012; Tremblay, 2014).

The General Aggression Model (GAM; DeWall & Anderson, 2011) states that cognitive factors within people influence how they perceive and interpret hostile situations, and consequently how they react. Cognitions in this regard can include beliefs about how people typically respond in certain situations (such as being insulted), expectations about the likelihood of various outcomes or how much they believe they can respond adaptively to a variety of events. An important focus of the GAM is that knowledge structures such as these influence both early and downstream psychological processes, and that they are developed based on the individual's experiences with aggressive situations. One possibility that may explain the increases in physical aggression in AAS users may be the development of certain expectations about physical aggression. One of the most commonly desired effect of AAS is the building of muscle mass and increase in physical strength(Cohen et al., 2007), an effect that has been thoroughly shown for use of AAS (Clark & Henderson, 2003; Evans, 2004; Ip et al., 2011). AAS users in our sample also reported significantly higher personal records in several strength training techniques. This increase in physical strength may over time lead to more successful utilization of physical aggression, i.e. more fights with an advantageous outcome, leading to positive expectations and beliefs about the use of physical aggression in goal-attainment. While one study found no increase in aggressive motivation in rats (Wood et al., 2013) the mechanism proposed above is a complex secondary effect that is probably unique to humans as animals do not hold conscious beliefs about the applicability of physical violence across situations. Future research should investigate the development of beliefs about physical aggression in long-term AAS users.

Anger was also significantly higher in AAS users. The anger-subscale of the BPAQ "involves physiologic arousal and preparation for aggression, [and] represents the emotional or affective component of [aggressive] behavior" (Buss & Perry, 1992). Anger has been conceptualized as an emotion (Smith, 1994) and a trait (e. g. Owen, 2010; Finkel et al., 2012) in that there is evidence for individual differences in the propensity to experience anger (Zelenski & Larsen, 2000). A higher level of trait anger has been associated with a higher frequency of encounters involving physical and verbal aggression (Tafrate, Kassinove & Dundin, 2002). One way in which higher trait anger can predispose people to aggress, is through a number of cognitive biases. High trait anger has been related to selective attention bias, favoring hostile stimuli, possibly a slight memory bias appraising past anger-provoking

events as more negatively than people with low trait anger, external attribution bias and other reasoning biases (Owen, 2010). These cognitive biases may also be hypothesized to contribute to the development of beliefs about physical violence proposed above. In the I^3-perspective, high trait anger may influence aggression by increasing the amount of instigating factors, that is provocative stimuli (through external attribution bias, selective attention toward hostile stimuli etc.) as well as be an impelling factor because high trait anger can lead to increased strength of the urge to act on aggressive impulses in hostile situations (Finkel et al., 2012). Taken together, this finding indicates that AAS users have a higher level of trait anger compared to non-AAS using controls, and may be prone to the associated cognitive biases. Furthermore, longer duration of AAS use, higher estimated life-time dose and earlier debut age were associated with higher levels of anger in AAS users. High trait anger in AAS users may be one of the explanations behind the increased levels of physical aggression seen in this group in both this and previous investigations.

A higher level of hostility was also seen in AAS users compared to controls. Higher hostility levels in AAS users have also been found previously (Pagonis et al., 2006a; Pagonis et al., 2006b; Hartgens & Kuipers, 2004). Participants in the earliest experimental study on AAS and aggression also showed elevated levels of hostility, although this difference only tended toward significance (Su et al., 1993). While there is somewhat of an overlap between anger and hostility, anger has been labeled an emotion (Smith, 1994), while hostility has been characterized as an attitudinal disposition, involving cynicism, mistrust and denigration of others (Miller et al., 1996; Birkley & Eckhardt, 2015). The higher scores on the hostility scale of the BPAQ thus may indicate that AAS users may be more cynical about their surroundings, and exhibit more mistrust toward other people. A higher level of hostility may impact frequency of physical aggression in a somewhat similar manner to anger; by increasing the number of situations interpreted as hostile, through both attributing ill will to other persons and provoking other people through denigration. In much the same way as trait anger, high levels of hostility may be another risk factor for physical aggression.

While group differences were found on the measures of physical aggression, anger and hostility, the difference seen on the verbal aggression scale only tended toward significance. This is somewhat puzzling, as one would expect most hostile social interactions that ultimately lead to physical aggression to begin with or at least also involve some form of hostile verbal exchange. This finding somewhat contradicts the findings of Pope, Kouri and Hudson (2000), who found no effects of AAS on any scales on the BPAQ *except* for the

verbal aggression subscale. One obvious methodological difference between experimental studies and the present is that duration of AAS use was significantly longer in the present investigation. The BPAQ has been used as a measure of *trait* aggression (e. g. Buss & Perry, 1992; Finkel et al., 2012). It should come as no surprise that a short term AAS career would lead to small or no changes on measures of aggression traits. Many items on the BPAQ measure beliefs about violence (e. g. "I can think of no good reason for ever hitting a person") or items that require experience with behaviors that for most people do not occur very often (e. g. "I have threatened people I know"). As this is a self-report measure, participants with the knowledge that they possibly have been given AAS would conceivably not endorse these items if their behavior only had changed recently. To support the notion that self-report measures of trait aggression are not the most appropriate method in investigations of short-term AAS use, participants in the study by Pope, Kouri and Hudson (2000) displayed significantly elevated levels of hostile responses on the PSAP, a behavioral paradigm intended to provoke aggressive behavior in the experimental situation.

As mentioned, many measures of severity of use correlated with higher levels of aggression. AAS users with a previous or current drug problem achieved significantly higher scores of aggression than AAS users without a history of drug abuse, who in turn achieved higher scores than controls (see fig. 4). As can be seen, AAS users without a previous or current drug problem are situated around the middle between controls and AAS users with a previous or current drug problem on all scales on the BPAQ.

The effects of combining AAS use with use of other illegal substances have been investigated in animals (Long et al., 1996; Steensland et al., 2005). These investigations also found that combining AAS with another illicit drug lead to higher levels of aggression than either substance alone. As can be surmised from previous studies and the results in the present study, there seems to be an additive or synergistic relationship between AAS use and use of other drugs of abuse on levels of self-reported aggression. While the relatively higher levels of aggression in AAS users with a previous or current drug problem mirrored that found in animal models (Long et al., 1996; Steensland et al., 2005), the mechanisms behind this relationship in humans probably extend beyond the neurochemical synergism proposed in animal models.

Involvement in drugs necessarily involves interaction with a criminal subculture of drug dealers and users. AAS users with a concomitant drug problem have reported other motives than increasing muscle mass for using AAS in other investigations, such as to

increase the intimidating qualities in order to avoid being taken advantage of and enabling the individual to take advantage of others (Cornford, Kean & Nash, 2014). Pope and colleagues (1996) interviewed a 27 year old man involved with drug dealing that partly used AAS in order to gain the confidence needed to deal drugs. Being part of a subculture like this might lead to higher levels of aggression as an adaptive response to the risk of being targeted by physical violence. Additionally, substance abuse use is closely associated with a wide range of psychopathology (e. g. Najt, Fusar-Poli & Brambilla, 2011).

The higher levels of aggression seen in AAS users without drug use, however, cannot readily be explained by the affiliation with a criminal subculture of illegal drug use or other psychological problems associated with drug abuse. This is interesting, as one explanation for the high levels of aggression in AAS users that has been proposed is the high prevalence of drug use in this group (Lundholm et al., 2014; van Amsterdam, Opperhuizen & Hartgens, 2011). The finding that AAS users without any history of drug abuse still display significantly higher levels of aggression than non-AAS using controls may lend support to the notion that this difference may be explained by the use of AAS in itself.

Estimated lifetime dose correlated significantly with anger and physical aggression. A dose-dependent relationship between AAS and levels of aggression has been found in the experimental studies investigating short term AAS use mentioned above (Pope, Kouri & Hudson, 2000; Su et al., 1993), but the results from the present study reveals a dose-dependent relationship between *lifetime* dose of AAS and several measures of aggression. One earlier investigation reported that "heavy" users suffer more severe psychiatric side effects, including aggression, than "light" users (Pagonis et al., 2006a). In this study, however, categorization within the three severity-groups depended not only on an estimated lifetime dose, but number of AAS-cycles completed, the number of different AAS-substances abused etc. The finding that estimated lifetime dose significantly correlated with aggression levels in AAS users may also lend support to the notion that higher consumption of AAS leads to higher levels of aggression. Duration of AAS use also showed an effect on several measures of aggression (see fig. 6). These two measures overlap somewhat, however, as duration of use was one of the factors taken into account when calculating estimated lifetime dose. Taken together, both these findings indicate that a more severe AAS using career is associated with higher levels of aggression compared to AAS careers involving less AAS consumption and shorter total use duration.

AAS users fulfilling the SCID-criteria for AAS dependency displayed higher levels of aggression compared to non-dependent AAS users. AAS dependent individuals reported significantly higher levels of physical aggression, anger and hostility than non-dependent AAS users. This finding may be a part of the general pattern that more severe use is associated with higher levels of aggression. A larger portion of AAS-dependent individuals were also classified as having a previous or current drug problem. An investigation directly comparing dependent and non-dependent AAS users also found AAS dependence to be related to comorbid psychopathology, a history of conduct disorder and opioid abuse or dependence (Kanayama, Hudson & Pope, 2009). These factors might form part of the explanation behind the higher levels of aggression see in AAS dependent individuals.

Considering the causal mechanisms behind the higher levels of aggression seen in AAS users, one explanation may be neurochemical alterations induced by AAS. As noted, use AAS has been associated with a range of neurochemical alterations in several brain regions implicated in aggression and the regulation of emotion in animal models (e. g. Henderson et al., 2006; Penatti, Porter & Henderson, 2009; DeLeon, Grimes & Melloni, 2002; Abdelgadir et al., 1999). The findings from the present study, when taken together, could be seen to lend support to the notion that AAS use induces higher levels of aggression. Firstly, estimated lifetime dose correlated significantly with levels of physical aggression and anger, as well as the total aggression measure, indicating that higher consumption of AAS was associated with higher levels of aggression. This would align well with the findings that chronic AAS use leads to alterations in neurochemical pathways associated with aggression (Henderson et al., 2009) and the neurochemical points of action for AAS in brain areas implicated in regulation of aggression and emotions (Abdelgadir et al., 1999; Sato et al., 2004; Scordalakes & Rissman, 2003). Secondly, while we did not have baseline aggression levels for the participants in this study, a majority (65.8 %) of AAS users reported aggression as a side effect of AAS use. Individuals with high baseline aggressiveness experiencing no further increase in levels of aggression following AAS debut would conceivably not attribute this high aggression level to AAS use. Thirdly, AAS users without any history of drug abuse obtained significantly higher scores on measures of aggression than controls. The higher levels of aggression seen in the AAS user group could not solely be explained by the high prevalence of concomitant drug use among AAS users. For this group of AAS users then, involvement in an illegal subculture of drug criminality or aggression levels induced by recreational drug abuse would not be an adequate explanation for higher levels of aggression.

Aside from neurochemical alterations induced by AAS substances, another possible mechanism behind higher levels of aggression in AAS users that deserves some consideration is social rejection. People that, due to various experimental manipulations, considered themselves socially rejected in various situations have been shown to experience negative emotions, and to denigrate the people they felt excluded them and sometimes become angry and aggressive (Buckley, Winkel & Leary, 2004; Twenge & Campbell, 2003). This increase in aggression following social rejection has been shown de directed both at the perceived excluders, but also at a neutral third party individual, unrelated to the exclusion of the individual (Twenge et al., 2001). Use of AAS is highly stigmatized, especially in sports, so it can be hypothesized that social rejection can be a common experience among some AAS users. As this possibility has not been explicitly investigated, this could be an interesting avenue for future research.

Taken together, the findings that several measures of AAS use severity correlated with levels of aggression, combined with previous animal research as well as the fact that many AAS users self-reported aggression as a side effect may lend support to the causal effect of AAS on aggression in humans. However, as we did not any data on baseline aggression levels in AAS users, firm conclusions regarding causality cannot be drawn from these findings alone.

5.3 Executive functions and aggression

The implications of the finding that AAS users perform worse than controls on measures of executive inhibition and executive control are of interest to the discussion about AAS and aggression. In our sample, AAS users displayed lower levels of executive inhibition and executive control and significantly higher levels of self-reported aggression, compared to controls.

As described in the introduction, impairments in executive functions have been implicated in higher levels of aggression, and possibly more strongly associated with violent crimes compared to other crimes (e. g. Hancock, Tapscott & Hoaken, 2010; Marsh & Martinovich, 2006). An interesting possibility that deserves some further consideration, then, is that lower executive functions in AAS users may be part of the explanation behind the association between AAS use and aggression. Especially the finding that AAS users display higher levels of trait anger and hostility are troubling, as a combination of these factors can be a treacherous concoction (Finkel et al., 2012).

While measures of inhibition in this investigation only slightly correlated with the total aggression scale of the BPAQ, the weakness of this correlation may be explained by the way aggression was measured. The only measure of aggression included in the present investigation was a self-report questionnaire, meaning that aggressive behavior *per se* was not gauged. Most studies investigating the association between executive functions and aggression have found this association in measures of aggressive behaviors (Finkel et al., 2012) or perpetration of crimes (Hancock, Tapscott & Hoaken, 2010). Future research should try to determine the association between executive functions and behavioral measures of aggression in AAS users utilizing behavioral paradigms or outcomes. One possible paradigm is the PSAP, which measures aggressive responding, operationalized as participants' preference for taking points from another player instead of gaining points for themselves in a faux multiplayer computer game. The study by Pope, Kouri and Hudson (2000) used the PSAP, and significantly higher levels of aggressive responding in AAS users, without significant differences on the BPAQ, indicating that there may be a discrepancy between these two measures of aggression.

5.4 Possible limitations

There are several limitations that must be held in mind concerning the present study.

One factor that may have led us to underestimate the levels of aggression in AAS users, is the sampling technique used for the present study. Participants were recruited from gyms and online AAS forums. As AAS use has been shown to be highly prevalent in prison populations (Lood et al., 2012; Lundholm et al., 2010; Beaver, Vaughn and Wright, 2008), our sample was conceivably somewhat biased as only AAS users not currently incarcerated were included. As incarceration rates conceivably are significantly higher among AAS using than non-AAS using exercisers, then our sample is not truly representative of the average AAS user. Aggression rates among incarcerated AAS user could be hypothesized as being higher than among users not currently in prison. However, as our investigation still found significantly higher levels of several aspects of aggression in AAS users, this may be seen as a testament to the robustness of this finding, rather than a detriment to the study design.

Another weakness with the design was the matter in which aggression was measured. Aggression was solely assessed using a self-reports. While the questionnaire shows good psychometric properties (Buss & Perry, 1992), self-reports of aggression are probably subject to social desirability bias considering how violence and aggression are highly socially

unacceptable behaviors (Saunders, 1991). To corroborate this notion, AAS users who had ceased using AAS rated themselves as more aggressive than their currently using counterparts. This may indicate either that current AAS users may have underreported their levels of aggression, that previous AAS users overrated their levels of aggression, or both. Aggression is probably one of the most commonly known adverse effects of AAS, conceivably making it vulnerable to underreporting in current users. One investigation also noted that correlations between testosterone levels and aggressiveness were stronger when aggressiveness was rated by others (Archer, 1991).

Another limitation with this investigation was that significance estimates were not corrected for by number of analyses performed. As the number of significance analyses in the present investigation was rather large, this may elevate the risk for type I errors. However, the majority of analyses were performed on measures of aggression which were quite robust. Concerning executive functions, a fewer number of analyses were performed, but significant results were not as robust as on measures of aggression.

The nature of the phenomena of interest in this investigation, might lead us to underestimate the effects of AAS. We are interested in the severity of certain negative side effects of AAS. One possibility, then, is that users who experience the most severe side effects discontinue AAS after a short while. Acute psychiatric effects of AAS have been shown to be highly variable between individuals (Su et al., 1993; Pope, Kouri and Hudson 2000). Some may display marked psychiatric symptoms following acute AAS use, while some display few side effects, if any. At this junction, then, many users who experience the most severe side effects, conceivably the individuals that are most reactive to AAS, might discontinue use of AAS due to a few bad experiences. Some, however, might not, weighing the benefits to muscular gain heavier than the negative side effects. The group of long-term AAS users, then, includes in this perspective two different classes of AAS users; those with a relatively benign reaction to AAS initially and users who have continued using AAS despite severe side effects. One interesting avenue for further research would be the developmental trajectories of side effects of AAS in users with a null- to mild reaction in the initial stages of their AAS use compared to those who are most reactive to AAS. Does long-term AAS use provoke negative side effects in subsamples of AAS users who initially experience no negative side effects, or are some AAS users blessed with a problem free AAS using career, independent of usage dose and duration? There is a lack of longitudinal follow-up studies of

side effect of AAS use. Such studies would be very informative in these matters, as well as for elucidating further the relationship between AAS, aggression and executive functions.

5.5 Conclusions

Taken together, the results from this study indicate that long-term AAS users display higher levels of anger, hostility and physical aggression than non-AAS using individuals, as well as poorer performance on some executive functions. Further, levels of aggression in AAS users were related to a more sever pattern of use, which may support the view that AAS play a causal role in forming aggression levels in long-term users. As this was a cross-sectional naturalistic observation study, firm conclusions regarding causality cannot be drawn from these findings alone, however.

While the results did not support the notion that AAS users perform worse than controls on task requiring cognitive flexibility, AAS users without a history of drug use performed significantly worse than controls on all measures of executive inhibition and executive control. As use pattern was not related to levels of executive functioning, however, the question remains open as to the reasons for these findings. A mix of reduced inhibition and heightened aggressiveness can be a dangerous combination that may be one of the explanations behind the higher levels of aggression observed in AAS users. As this is the first time long-term AAS use has been related to poorer performance on measures of executive inhibition, there is a pressing need for further investigations of this association.

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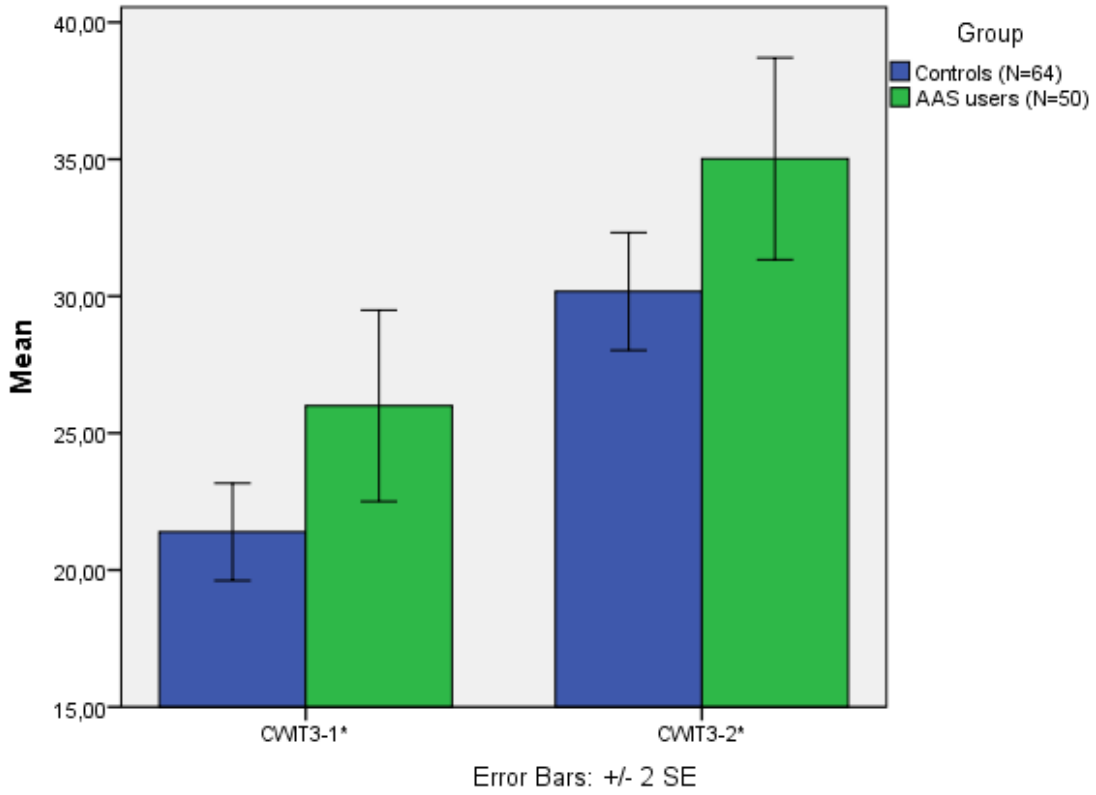
Appendix

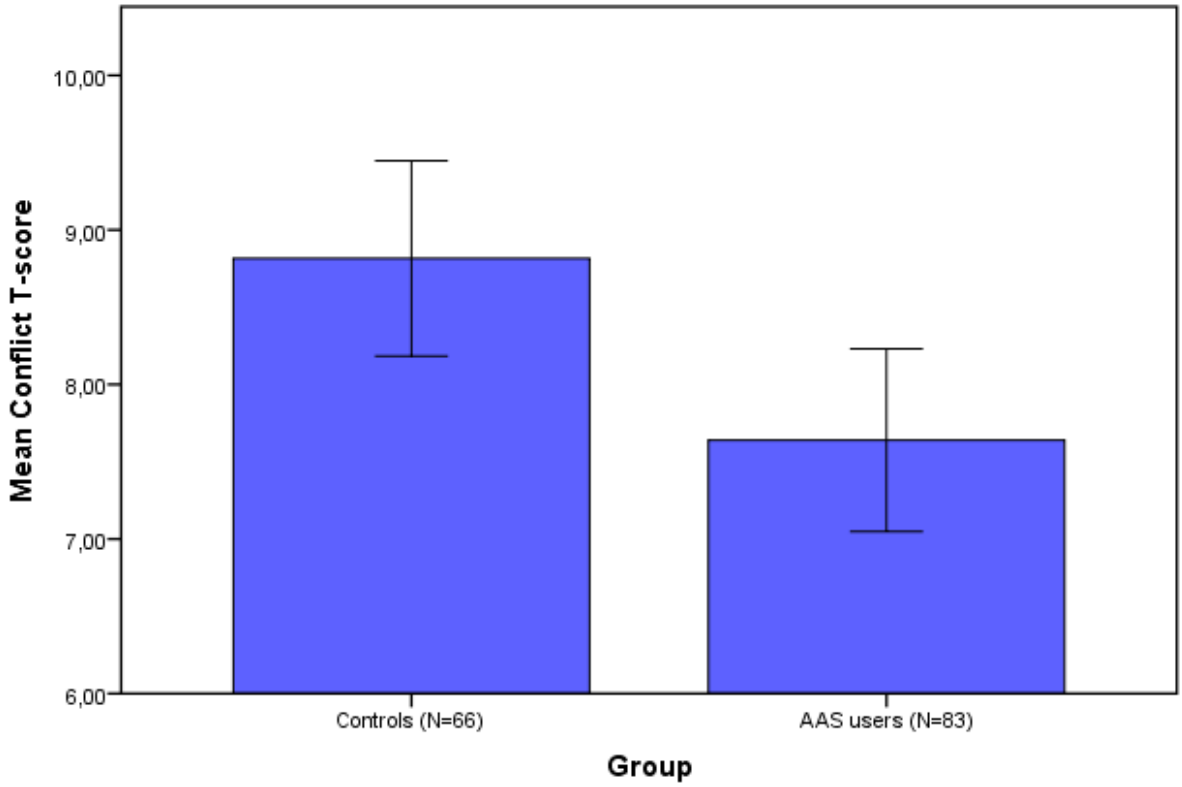
A.1 Figures

Fig. 1 Mean scores for participants without a history of drug abuse on measures of executive inhibition



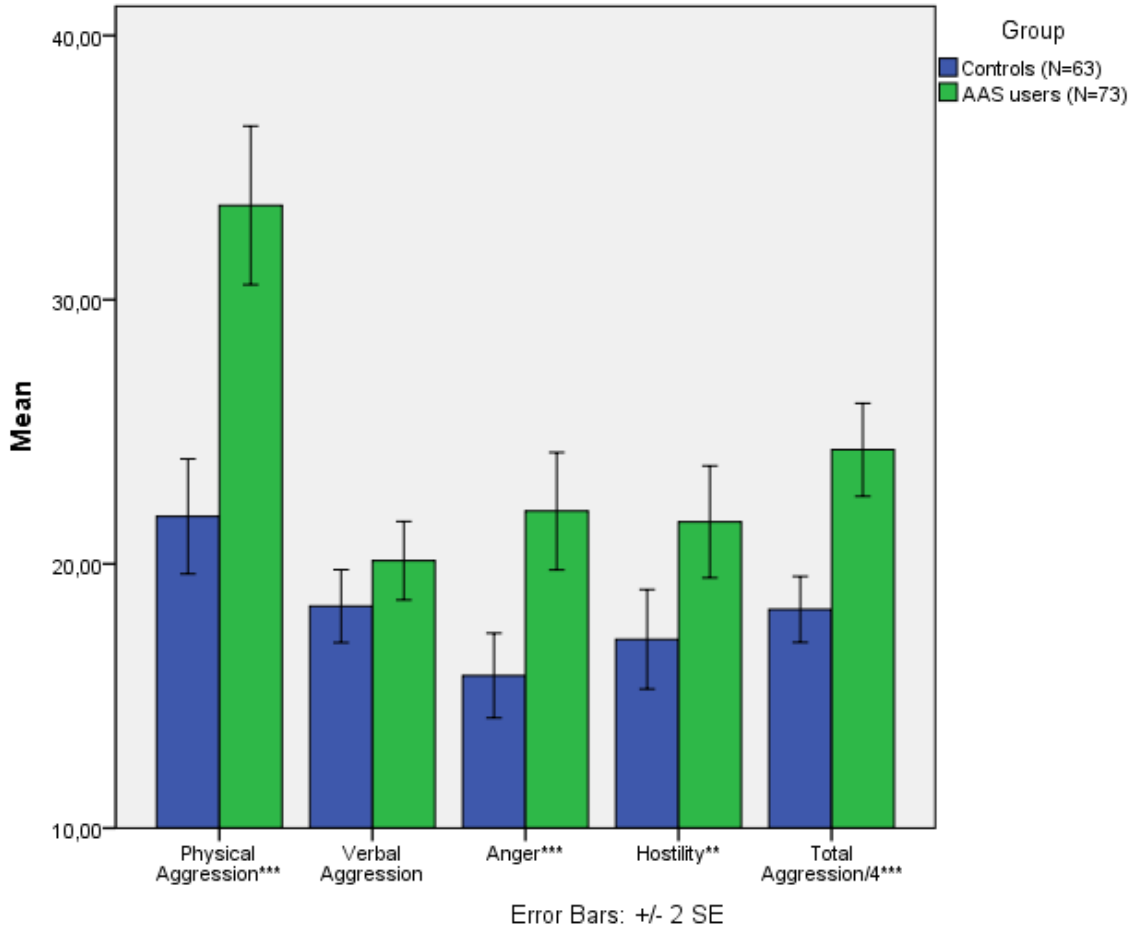
Mean scores for controls (N=64) and AAS users (N=50) without a history of drug abuse. * indicates a significant difference at the <.05-level. The differences between the CWIT3-1 and CWIT3-2 can be attributed to a learning effect as well as the novelty of the first condition compared to the second, meaning that the completion times are longer for the first condition.

Fig. 2 Mean scores on the conflict measure of the ANT



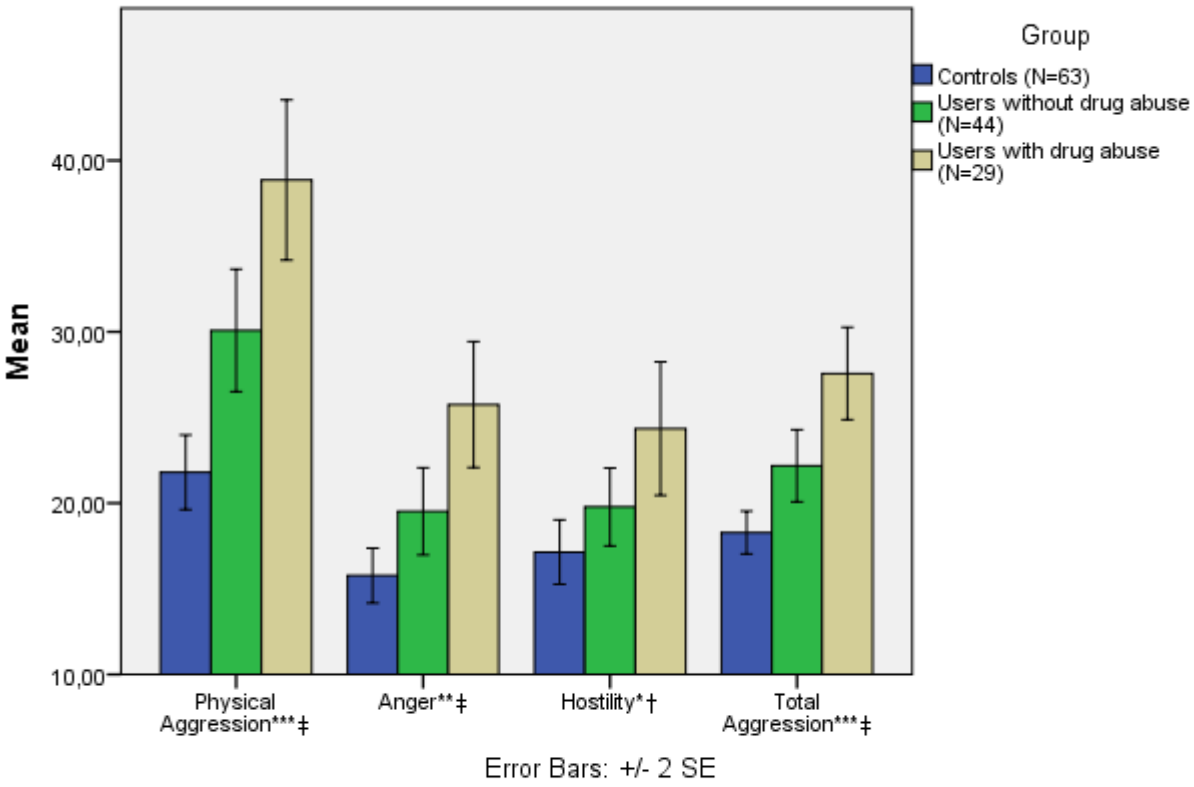
Mean T-scores for controls (N=66) and AAS users (N=83) on the conflict measure of the Attention Network Test. A higher score on this condition represents faster reaction times on incongruent versus congruent stimuli in the ANT. Controls scored significantly higher than AAS users on this measure.

Fig. 3 Mean scores for controls and AAS users on scales of the BPAQ



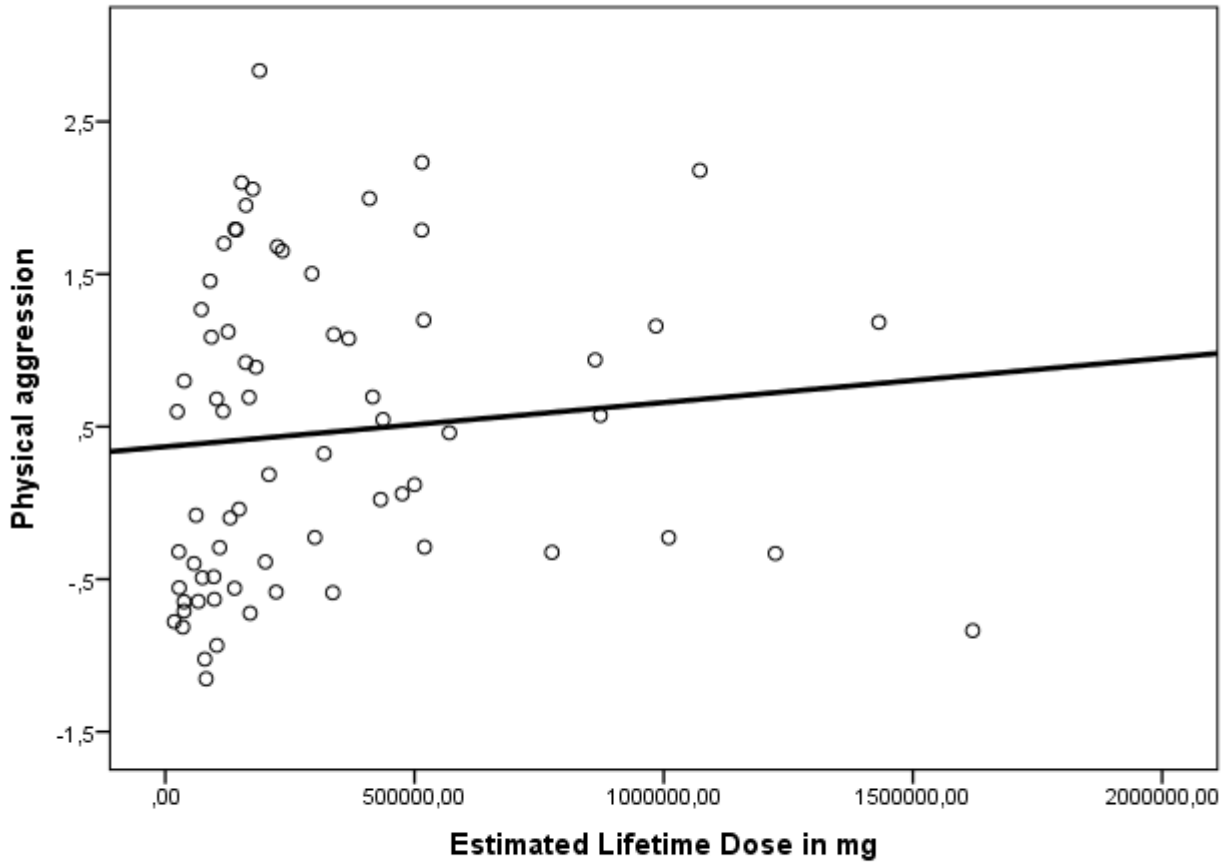
Mean scores on the scales of the Buss Perry Aggression Questionnaire for controls (N=63) and AAS users (N=73). ** indicates a difference significant at the <.01-level and *** indicates significance at the <.001-level.

Fig. 4 Mean scores for controls and AAS users without and with a history of drug abuse



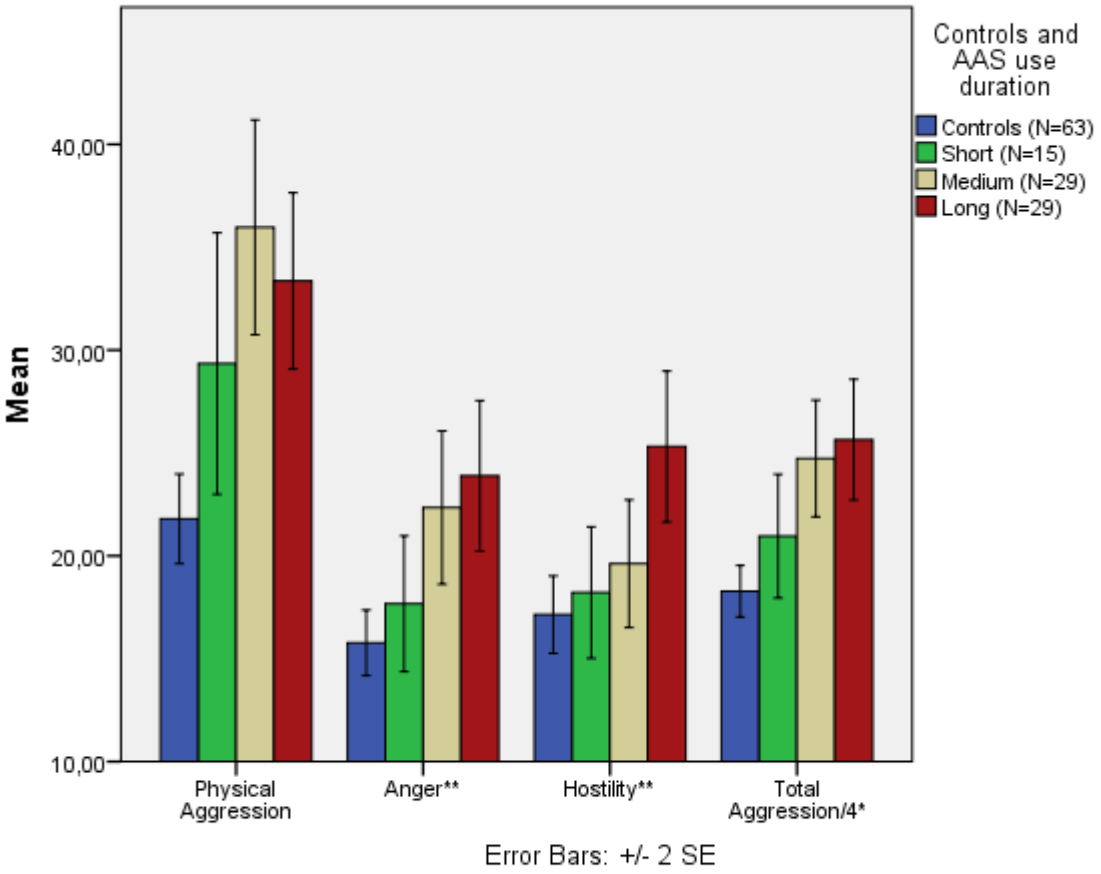
Mean scores for controls (N=63), AAS users without (N=44) and AAS users with (N=29) a previous or current drug problem. * indicates a difference between controls and AAS users without a previous or current drug problem significant at the <.05-level, ** indicates this significance at the <.01-level and *** at the <.001-level. †indicate a difference between AAS users with and without a previous or current drug problem significant at the <.05-level, ‡ indicates that this difference is significant at the <.01-level.

Fig. 5 Physical aggression and estimated lifetime dose in mg



Estimated lifetime dose and physical aggression. Variability associated with age is removed as physical aggression scores are plotted as z-transformed residuals. Please note that one AAS user is removed from this scatterplot as his estimated life-time dose was close to 4,000,000 mg.

Fig. 6 Scores on the BPAQ for controls and users with varying use duration



Mean scores for controls (N=63) and AAS users with short- (N=15), medium- (N=29) and long-term (N=29) AAS use. * indicates a main effect of use duration significant at the <.05-level, ** indicates this significance at the <.01-level.

Fig. 7 Self-reported side effects of AAS

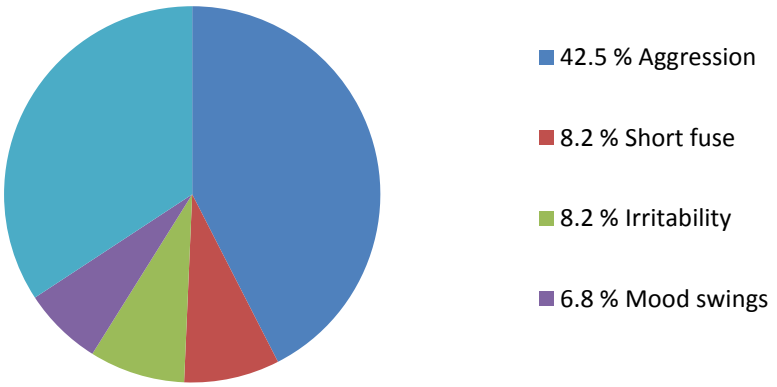
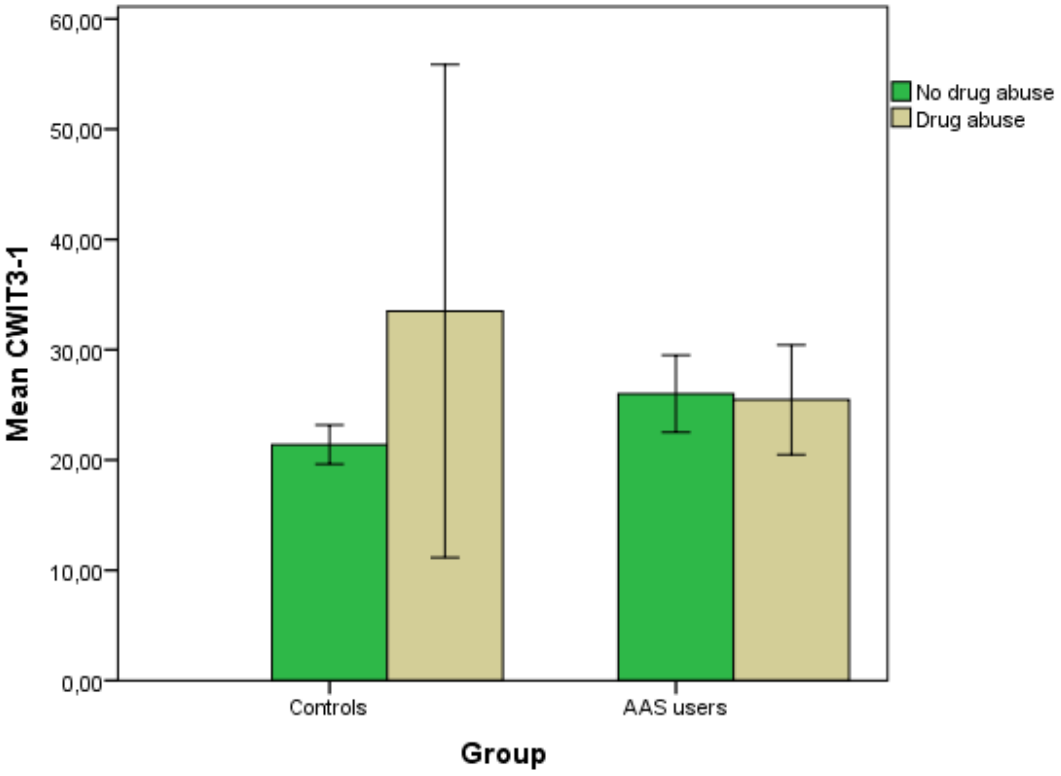


Fig. 8 Controls and AAS users with and without a history of drub abuse on the CWIT3-1



Mean scores on the CWIT3-1 contast measure for controls and AAS users with (Controls; N=4, AAS users; N=34) and without (Controls; N=64, AAS users; N=50) a previous or current drug problem.

A. 2 Tables

Table 1 **Descriptive statistics**

	Group	Minimum	Maximum	Mean	Std. Deviation
Age	Controls	19,0	75,0	31,8	9,5
	AAS users	21,0	56,0	33,5	8,5
Education level**	Controls	9,0	22,0	15,8	2,7
	AAS users	9,0	21,5	14,1	2,5
Strength sessions per week	Controls	2,0	12,0	4,7	1,5
	AAS users	0,0	17,5	4,5	2,3
Minutes spent on strenght exercise per week*	Controls	120,0	1200,0	463,2	242,1
	AAS users	0,0	1265,0	348,8	204,1
Endurance sessions per week	Controls	0,0	6,0	1,5	1,6
	AAS users	0,0	11,0	1,8	2,3
Minutes spent on endurance exercise per week	Controls	0,0	600,0	90,7	112,5
	AAS users	0,0	990,0	122,9	191,9

Tbl. 1 Descriptive statistics for controls and AAS users. * indicates a significant difference at the <.05-level. ** indicates a significant difference at the <.01-level.

Table 2

Differences between controls and AAS users on the BPAQ			
BPAQ Scale	Group	Mean	Std. Deviation
Physical Aggression***	Controls	21,80	8,64
	AAS users	33,57	12,82
Verbal Aggression	Controls	18,40	5,48
	AAS users	20,12	6,34
Anger***	Controls	15,77	6,35
	AAS users	22,00	9,50
Hostility**	Controls	17,14	7,47
	AAS users	21,59	9,05
Total Aggression***	Controls	73,11	19,85
	AAS users	97,28	30,11

Tbl. 2 Group differences on the BPAQ. ** Indicates significance at the <.01-level, *** indicates significance at the <.001-level.

Table 3

Scores for controls and AAS users without previous or current drug problem			
BPAQ Scale	Group	Mean	Std. Deviation
Physical Aggression***	Controls	21,11	8,08
	AAS users	30,08	11,85
Verbal Aggression	Controls	18,26	5,56
	AAS users	19,34	6,28
Anger**	Controls	15,47	6,39
	AAS users	19,52	8,45
Hostility*	Controls	16,74	6,90
	AAS users	19,78	7,56
Total Aggression***	Controls	71,58	18,21
	AAS users	88,72	27,95

Tbl. 3 Group differences on the BPAQ.* Indicates significance at the <.05-level, ** indicates significance at the <.01-level and *** indicates significance at the <.001-level.

A. 3 Miscellaneous

Syntax for Non-parametric Partial Correlation Analysis in SPSS:

```
DATASET ACTIVATE DataSet1.
NONPAR CORR
  /VARIABLES= *Variable names (including covariates)*
  /PRINT=SPEARMAN TWOTAIL NOSIG
  /MISSING=LISTWISE
  /MATRIX=OUT(*).
RECODE rowtype_ ('RHO'='CORR') .
PARTIAL CORR
  /VARIABLES= *Variable names* BY *Covariate Variable Names*
  /SIGNIFICANCE=TWOTAIL
  /MISSING=LISTWISE
  /MATRIX=IN(*).
```

N.B. The covariate(s) to be used in the partial correlation analysis has to be included among the variables in the first analysis.